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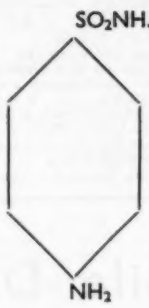

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ADDRESSES AND ORIGINAL ARTICLES

A RATIONAL APPROACH TO RESEARCH IN CHEMOTHERAPY

By Paul Fildes, O.B.E., M.B.Camb., F.R.S.
DIRECTOR OF THE DEPARTMENT OF BACTERIAL CHEMISTRY, MEDICAL RESEARCH COUNCIL

(*From the Bland-Sutton Institute of Pathology, and from Courtauld Institute of Biochemistry, Middlesex Hospital*)

Several authors have expressed the view recently that the action of sulphanilamide in vivo depends on an interference with some bacterial enzyme reaction which is necessary for the growth of the organism. Lockwood (1938), for instance, thought that proteolytic enzymes of streptococci are inhibited, but since such enzymes are unknown in the case of this organism, and in any event are demonstrably not necessary for growth, the basis for such a view appears to be slight. McIntosh and Whitby (1939) thought that sulphanilamide might act by blocking the vital food-supply of bacteria by inactivating an enzyme. Stamp (1939) extracted from streptococci a substance which antagonised the action of sulphanilamide and concluded that this extract might contain a necessary nutritive factor, the production of which was interfered with by sulphanilamide. The nutritive factor might be of the nature of a co-enzyme. Green (1940), who also obtained an extract from bacteria which counteracted the action of sulphanilamide, concluded that the latter acted by inhibiting an enzyme reaction fundamental in the metabolism of bacteria and that the active substance in his extract stimulated it. Finally Woods (1940) has obtained an extract from yeast which counteracted the action of sulphanilamide and has identified the active material as *p*-aminobenzoic acid. This substance is looked upon as an "essential metabolite" with which sulphanilamide interferes as will be discussed later. These authors are thus in agreement in ascribing the action to interference with bacterial enzymes associated in some way with nutritive substances.*

The wider aspects of inhibition of bacterial growth have been the subject of study in this department for a number of years, following as a natural sequence on our studies of bacterial "growth factors," and evidence has been accumulating that inhibition of bacterial growth in general may be exerted through interference with one of these "factors." Since the definition of a growth factor has tended to become modified it will be necessary for a proper understanding of the theory of interference to outline our present views on this subject.

BACTERIAL GROWTH FACTORS

The growth and multiplication of bacteria (and no doubt of all cells) involves the synthesis of new bacterial substance from simpler compounds. In the case of protein the simplest compound is ammonia and from this and a suitable source of carbon some bacteria can synthesise protein, the energy required in the process being liberated from a combustible material such as glucose. Although little or nothing is known about the mechanism of this synthesis, it is inferred that it is achieved in steps by a series of enzymes operating on each stage as it is completed.

The main evidence in support of this view is that whereas *Bacterium coli* can grow (i.e., synthesise all its nitrogenous compounds) from ammonia, *Bact. typhosum* cannot, except when certain amino-acids which are constituents of protein are added. The amino-acids which must be supplied to *Bact. typhosum* are demonstrably synthesised by *Bact. coli*, and it is concluded that the failure of *Bact. typhosum* to grow from ammonia is due to a failure to synthesise the amino-acids. These amino-acids which must be added to the nutrients are "growth factors" for *Bact. typhosum*. They represent stages in the synthesis of protein which *Bact. typhosum* cannot achieve, but it will be understood that these stages are equally present in the syntheses carried out by *Bact. coli*, though in this case they are not growth factors since the organism can synthesise them. Each stage in any synthesis necessary for growth is referred to as an "essential metabolite," without which, either synthesised or supplied from outside, growth cannot occur. A growth factor is thus an essential metabolite which cannot be synthesised. The requirement by a particular species for an essential metabolite to be given as a growth factor is not characteristic for the species. Some strains can synthesise it more or less or can be induced to do so. At the moment the view is gaining ground that the essential metabolites at present known in bacteriology, or at any rate many of them, are common to all or most cells whether bacterial or not.

Although the process of growth has been represented as a building up of bacterial protoplasm, there are other processes to be carried out subsidiary to this main object. For instance the process by which energy is set free must be catered for. This involves the synthesis of various co-factors which take part in the process. Thus cozymase, a substance of known composition containing nicotinic acid, is a constituent probably of all cells and is associated with the process by which glucose, for instance, is combusted. Since *Bact. coli* grown on ammonia contains cozymase it is concluded that it can synthesise it from ammonia. On the other hand *Proteus vulgaris* can only grow from ammonia when cozymase is added, showing that the failure to grow is due to a failure to synthesise cozymase. Actually the failure is due only to failure to synthesise the nicotinic acid fraction of cozymase, since when this alone is added growth will occur. The other constituents of the cozymase molecule can be synthesised. *Bact. typhosum* cannot grow from ammonia, even when cozymase is added, but it can grow from amino-acids when no cozymase is added, and thus can synthesise all fractions of the cozymase molecule from amino-acids. Staphylococcus can only grow from amino-acids if nicotinic acid is added. *Hæmophilus influenzæ* is different in that, though it is given nicotinic acid, it cannot finish the synthesis of cozymase and must be supplied with the final product ("V" factor of the bacteriologists). Thus cozymase is an essential metabolite for all these bacteria, but it is a growth factor only for *H. influenzæ*, while nicotinic acid, a stage in the synthesis of cozymase, is a growth factor for proteus and staphylococcus. These relationships are indicated in the figure:—

SYNTHESIS OF COZYMASE

NH_3 ——→ Amino-N ——→ Nicotinic acid ——→ Cozymase
(Stage 1) (Stage 2) (Stage 3)

Essential metabolite—
Stage 1 = growth factor for *Bact. typhosum*
„ 2 = „ „ staphylococcus and proteus
„ 3 = „ „ *H. influenzæ*

It will, of course, be understood that the direct discovery of an essential metabolite can only be made in the case of a bacterium for which it is a growth factor—i.e., which cannot synthesise it. In addition to the many growth factors which have been described already, it is presumed that there are others which cannot be detected until a bacterium is found which cannot synthesise them.

* Fleming (1940) showed that suspensions of a number of bacteria in a solution of sulphanilamide, even when dead, counteracted the action of the drug. The effect was due to substances given off by the bacteria under these conditions.

Bacteria (and other cells) are thus looked upon as organisms which are potentially able to synthesise their structure and accessory reagents from simple compounds, though many as a result of altered environment have more or less lost the power to carry out one or more stages of essential syntheses (cf., Lwoff 1932, Knight 1936). In such cases the particular stage of synthesis which fails becomes a growth factor which must be added to an artificial nutrient mixture or borrowed from a host which has either synthesised it itself or ingested it in its nutrients. Whether, however, an organism can synthesise the stage or not it remains an essential metabolite, interference with which will inhibit growth.

MECHANISM OF BACTERIAL INHIBITION

The evidence on which we have been led to associate bacterial inhibition with interference with essential metabolites is broadly as follows.

Fildes (1929) and Knight and Fildes (1930) showed that anaerobes would not grow if the oxidation-reduction potential of the medium was maintained positive to a certain level. In less technical language this implies that anaerobes will only grow when a certain degree of reducing intensity is present in the medium. If the degree of reducing intensity is diminished by oxygen or by an oxidising agent such as ferricyanide, thionine or methylene-blue no growth takes place until these have been reduced. The metabolism of an anaerobe is "anaerobic"—i.e., it involves the presence of reduced substances in the nutrients or at least an absence of oxidising substances. A similar inhibiting effect of thionine or methylene-blue is also observed with aerobes, for the reason that conditions *within* an aerobic cell are anaerobic and a sufficient concentration of these diffusible dyes imposes aerobic conditions within the cell.

This subject was discussed by Fildes (1937), who pointed out that the inhibition was only observed with diffusible dyes and not with non-diffusible dyes of a similar oxidising capacity. It was concluded that the inhibition was due to oxidation of some substance within the cell, which in metabolism required to be reduced. In more recent phraseology it was due to an interference by oxidation with an essential metabolite which required to be reduced in order that the enzyme associated with it might function normally as in growth.

At this stage a number of essential metabolites had been isolated, and in particular the group -SH was known to be necessary for staphylococci (Fildes and Richardson 1937) and moulds (Volkonsky 1932). In view of the fact that H-SH combines with mercury, and H-SH reverses the antibacterial action of mercury was it possible that the antibacterial action of mercury was due to combination with essential -SH groups within the cell? This subject has been dealt with recently by Fildes (1940). He showed that mercury combined in the test-tube with -SH in certain molecular proportions to form a soluble compound devoid of -SH. This compound was not in itself inhibitory. Inhibition was only observed when mercury in a mixture of mercury and -SH was in excess of the molecular proportions noted. It was concluded that the antibacterial action of mercury was due to the diffusible salt entering the cell, thus depriving it of an essential metabolite. And in the concentrations used this was the only action of mercury, since addition of excess of -SH allowed the inhibited organisms to grow normally—i.e., excess of the essential metabolite did away with the inhibition.

MODE OF ACTION OF SULPHANILAMIDE

With the introduction of the sulphanilamide drugs, it became a question whether the same argument could not be applied and in this matter we were able to profit by the experience of McIntosh and Whitby. Prolonged experiments were carried out to test whether any known essential metabolite could be associated with the action of sulphanilamide, in the sense that a quantitative relationship could be shown to exist between the inhibitory concentration of sulphanilamide and the counter-action of the essential metabolite. These experiments were unsuccessful. At this stage Stamp (1939) showed that he was able to reverse the action of sulphanilamide by an extract obtained from streptococci. We assumed at once (as also did Stamp) that this extract contained an essential metabolite which was not a growth factor for streptococci, since at this time all these were known (McIlwain 1940). As has been explained we do not look upon essential metabolites as specific to one species of bacterium or even to bacteria at all, and thus for convenience made extracts from yeast following more or less the procedure of Stamp. The result of this work has been published by Woods (1940). By fractionation of yeast extracts he obtained a material with well-defined chemical characters which reversed the action of sulphanilamide. This material could not for quantitative reasons combine with sulphanilamide on a molecular basis as does -SH with mercury, but it might act by competing with sulphanilamide for an enzyme of which it was the natural substrate. In this case it should follow that the substance in the extract had some structural similarity with sulphanilamide, and it became a question as to what substance similar to sulphanilamide had the chemical characters of the extract substance; *p*-aminobenzoic acid was tried and was found to antagonise sulphanilamide quantitatively and in very high dilutions. At the moment, therefore, it is supposed that *p*-aminobenzoic acid is an essential metabolite for bacteria, although for technical reasons it has not yet been isolated from them nor has it yet been proved to be a growth factor in the absence of a bacterium which cannot synthesise it This essential metabolite is normally associated with an enzyme, and sulphanilamide, being structurally similar to it, is capable if in sufficient concentration of displacing *p*-aminobenzoic acid from its enzyme and stopping this essential line of metabolism.

On this view the "sensitivity" of a microbe to sulphanilamide would depend at least in part upon whether it could synthesise *p*-aminobenzoic acid readily or not. An organism whose synthetic powers were poor would be more sensitive than one with greater power. Similarly a large number of bacteria would be less affected by a certain concentration of sulphanilamide than a small number. Inhibition or not would become a question of the proportion of sulphanilamide to *p*-aminobenzoic acid affecting the enzymes of each cell.

It is of interest that *p*-aminobenzoic acid also antagonises sulphanilamide in vivo (Selbie 1940), so that animals die from a streptococcal infection in the presence of a curative dose of sulphanilamide when *p*-aminobenzoic acid also is added.

Since, in our view, *p*-aminobenzoic acid is an essential metabolite not only for bacterial cells but also for animal, curative interference with it in vivo will affect both bacterium and host. Success in treatment must then depend upon the relative "sensitivity" of the two types of cell or upon whether the host as a whole can survive the inhibition of this enzyme reaction for sufficiently long. It is possible that this inhibition may account for some of the later toxic effects of sulphanilamide. These effects might then be looked upon as due to a deficiency in *p*-aminobenzoic acid and might be treated by administration of this deficient substance.

LINE FOR FUTURE RESEARCH

If further work confirms the conclusions drawn from experiments with the three different antibacterial agents, dyes, mercury and sulphanilamide—that the antibacterial actions are due to specific interferences with essential metabolites—it should follow that an antibacterial substance should be capable either of combining with an essential metabolite to form a product devoid of the essential metabolic function, or of blocking an enzyme specifically associated with the metabolite. In this latter case it is to be expected that the antibacterial substance should have a chemical similarity to the essential metabolite. Chemotherapeutic research might then reasonably be directed

to modification of the structure of known essential metabolites to form products which can block the enzyme without exhibiting the specific action of the metabolite. It is curious to note that chemists are already to some extent proceeding along these lines. In sulphapyridine, for instance, the base attached to the sulphanilamide is related to nicotinic acid, and in sulphathiazole to vitamin B_1.

SUMMARY

An "essential metabolite" is a substance or chemical group which takes an essential part in a chain of syntheses necessary for bacterial growth. A "growth factor" which must be supplied in the nutrients is an essential metabolite which the cell cannot synthesise. Nicotinic acid, for instance, is an essential metabolite for all bacteria but a growth factor for only a few.

Antibacterial substances function by "interfering" with an essential metabolite and thus inhibit growth. The interference may be (1) by oxidising a substance which requires to be reduced, (2) by molecular combination forming an inactive product, or (3) by competition for an enzyme associated with the essential metabolite. It is claimed that sulphanilamide acts as in (3), the essential metabolite being *p*-aminobenzoic acid. Class (3) inhibitions require an inhibitor so closely related in formula to the essential metabolite that it can fit the same enzyme, and sufficiently unrelated to be devoid of essential metabolic activity. It is suggested that research in chemotherapy might reasonably be directed to making such modifications of known essential metabolites as will have these characters.

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TREATMENT OF FRACTURES OF UPPER THIRD OF SHAFT OF FEMUR

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I have recently seen several similar cases of closed transverse fractures of the shaft of the femur close to the junction of the middle and upper thirds in young healthy adults. In each one there was a history of treatment by skeletal traction in a Braun's splint for some months after the injury. Accurate reduction was never obtained, and union in a faulty position was slow. Ultimately the patients were allowed to walk wearing a calliper. In spite of the calliper bending took place at the site of the fracture; in one case there was complete redisplacement of the fragments. Open operation with reduction and plating was next resorted to. There followed a period of months when union was not firm enough to permit of weight-bearing, and the patients were again allowed to get about wearing a walking calliper. On examination at this stage, although from twelve months to two and a half years had elapsed since the date of original injury, the prognosis in each case was still in doubt. Study of the histories and serial radiograms of these cases indicated that a common factor had influenced the results.

DEFORMITY

In a fracture of the shaft of the femur close to the junction of the middle and upper thirds there is a typical displacement—flexion and abduction of the upper fragment, due to the action of the psoas and short muscles inserted on the great trochanter, with posterior inward and upward displacement of the lower fragment, due to the action of the hamstring and adductor muscles (fig. 1). The reduction and immobilisation of this fracture is best effected by skeletal traction, with a Kirschner wire passed through the upper end of the tibia, the limb being supported with a suitable splint. Since the upper fragment is short and cannot be controlled, traction should be applied in the line of this fragment—i.e., with the leg abducted and flexed at the hip. The flexion deformity of the proximal fragment is usually about 50°. If a Braun's splint is used, the amount of flexion at the hip must be constant and is about 30° (fig. 2).

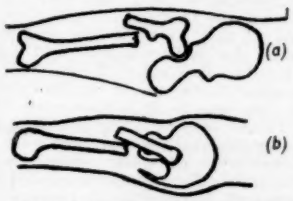

Fig. 1—Diagrams of deformity produced by fracture of the upper third of the shaft of the femur: (*a*) anteroposterior view; (*b*) lateral view.

In advocating the use of a Braun's splint for this type of fracture Böhler (1935) says "flexion of the upper fragment will disappear when shortening is corrected," but he offers no reason for this. The flexion is due to the postural tone of the psoas and pectineus muscles and, with an intact femur, is counterbalanced by the gluteus maximus and hamstring muscles. Of these only a quarter of the gluteus maximus is inserted on the upper fragment, and this is the least effective part of the extensor mechanism. There seems to be no reason to suppose that the postural tone of the psoas and pectineus muscles should be abolished by a simple distraction of the shortening which has taken place.

Fig. 2—Diagram of amount of flexion (30°) produced at the hip when a Braun's splint is used.

If this flexion deformity is not corrected, the bone ends are left in an unsuitable position for union, because the raw surfaces are not in apposition (fig. 3), and union, when it does take place, is mechanically unsound, because weight-bearing exposes it to a shearing force (fig. 3*b*).

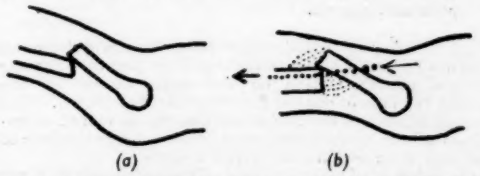

Fig. 3—Diagrams of results of uncorrected flexion deformity: (*a*) non-union; (*b*) unsound union liable to shearing force (indicated by arrows).

SPLINTS

The use of the Braun's splint, as recommended by Böhler for the treatment of all types of fractures of the shaft of the femur, is becoming increasingly common, to the exclusion of the Thomas type of splint. This is probably due to two factors: (1) the teachings of the Vienna school represent such a general advance in the treatment of fractures that

there has been a tendency on the part of surgeons in this country to accept them in toto to the exclusion of all other methods; and (2) a Braun's splint can be used by itself, without the necessity for slinging from an overhead beam. It is consequently a cheaper and more compact piece of apparatus than the Thomas type of splint slung from a Balkan beam, and it is less trouble to adjust than the latter. In fact it represents the "easy way" of treatment. Nevertheless for fractures of the type described the "easy way" may prove in the long run the most troublesome for both surgeon and patient. In the cases already mentioned flexion of the short proximal fragment was never adequately corrected, and this flexion was in each case more than can be obtained by immobilising a leg in a Braun's splint.

By skeletal traction and with a Thomas or Robert Jones type of splint with a bent-knee attachment, slung from a Souttar's modification of the Balkan beam, it is possible to procure traction in the long axis of the femur with the hip in any degree of flexion required. Moreover, by proper adjustment and slinging of the splint it is possible to maintain this traction in the same axis while lifting a patient for a bedpan or for attention to the back.

TREATMENT

The results of treatment of fractures of the femoral shaft of the type described are excellent when this apparatus is used and attention is paid to the following points:—

(1) *Fitting of ring at upper end of splint.*—This should fit closely round the thigh and should bear on the posterior surface of the tuberosity of the ischium. These are most important points. A loose ring tends to slide up and down and shift from side to side, chafing the skin. When the ring bears on the posterior surface of the tuberosity of the ischium, the upward pull of countertraction is transmitted to the pelvis (fig. 4*a*); whereas, if it bears on the femur below the tuberosity, this pull increases the flexion deformity of the proximal fragment (fig. 4*b*).

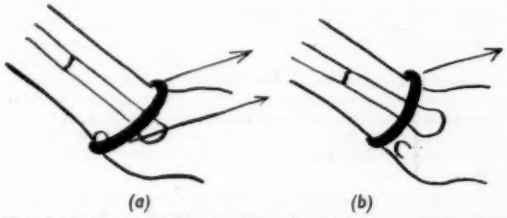

FIG. 4—Diagrams of fitting of the ring at the upper end of a Thomas splint: (*a*) with the ring bearing on the posterior surface of the tuberosity of the ischium, the pull of countertraction is transmitted to the pelvis; (*b*) with the ring bearing on the femur below the tuberosity, the pull of countertraction increases the flexion deformity of the proximal fragment.

(2) *Slinging of splint.*—The splint is slung from an overhead beam with two double pulleys (fig. 5). By this method countertraction on the splint caused by the weight (W) is kept constant and equally distributed. The patient is lifted in the line of traction on the femur, movements of the splint being compensated by movement of the ring from which the weight is slung.

(3) *Slinging of leg from splint.*—The leg should be slung with strips of flannel fastened with clips at each side. If the leg is slung with one clip, as is the common practice, when the flannel sags, it can only be tightened from one side, and the leg is rotated.

(4) *Skeletal traction* is best effected with a Kirschner wire passed through the tibial tuberosity. Watson-Jones (1940) has pointed out the disadvantages of using a wire passed through the lower end of the femur. From a horseshoe a cord passes over a pulley (fig. 5). Flexion at the hip-joint is regulated by raising or lowering this pulley, with suitable adjustment of the bent-knee attachment and the weight (w).

(5) *Reduction of fracture.*—Deformity is reduced by varying the force and axis of traction. It is convenient to start with a weight of a seventh of the body-weight of the patient. Position is checked by radiography after twenty-four hours, and traction is adjusted according to the degree of overlap. At the same time the degree of flexion and abduction at the hip is adjusted, so that traction is in the line of the short proximal fragment. It is important to remember that, as soon as overlap is corrected, the

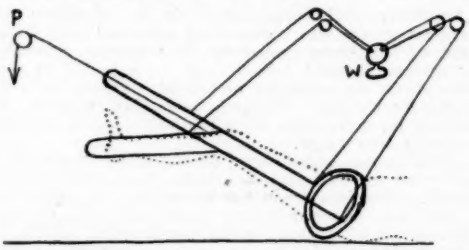

FIG. 5—Diagram of the slinging of the splint (see text): P, pulley; W, weight.

traction should be reduced until it is just sufficient to prevent recurrence of the deformity. If this is not done, separation of the fragments is produced and, if allowed to persist, will cause non-union. Countertraction is provided by raising the foot of the bed on blocks, thus utilising the patient's weight, and by the weight (w), which should be sufficient to support the leg with the hip flexed at the required angle and varies from 4 to 8 lb. according to the size of the patient and the degree of flexion at the hip. When reduction is satisfactory and no change in position has taken place for forty-eight hours, further radiography is only necessary once a week for four weeks, then once every four weeks until firm union has taken place. By these methods it is rarely necessary to resort to lateral pressure to achieve accurate reduction.

(6) *Routine checking of position by radiograms* has already been referred to but may be summed up as follows: examination every twenty-four hours until accurate reduction has been achieved and maintained for forty-eight hours; then examination every seven days for four weeks; then every four weeks until union is firm.

(7) *Union.*—If accurate reduction has been achieved and distraction of the bone ends avoided, firm union is to be expected in three to four months. When on clinical and radiological grounds it has been decided that union is firm, the wire is removed and the leg is allowed to remain in the splint without traction for a week. A further radiogram is now taken, and, provided position is unchanged and no untoward symptoms have developed, the splint is removed, and the patient remains in bed for a further week. If a second examination is then satisfactory, the patient is allowed to get up and begin weight-bearing with the aid of a stick.

(8) *Physiotherapy.*—From the first the patient is instructed to move his patella by contracting his quadriceps muscle. This quadriceps drill should be practised five minutes every hour or so. Movements at the knee should be begun at the end of the first week, and the knee should be put through as full a range of movements as possible three times a day. If this is done, there should be little wasting of muscle and a fair range of movement at the knee when the patient is able to get up. Massage exercises and, if necessary, faradism to the quadriceps muscle are then begun and continued for a few weeks.

(9) *Drugs.*—The main factor in producing firm union is early and accurate reduction of bony displacement with subsequent effective immobilisation of the limb. No amount of therapy can compensate for failure to achieve these requirements. If the patient is undernourished or anæmic, however, the administration of vitamins, calcium, and iron is beneficial, and in the ordinary case these can do no harm.

(10) *Regular examination.*—The splint should be examined daily and any necessary adjustments made.

(11) *Coöperation of patient.*—It is always worth while to attempt to get the patient to take an intelligent interest

in his splint. With this type of apparatus a patient can keep the upper ring of the splint well pulled up and, by twisting this ring, can correct any rotation of the leg. The success of the quadriceps drill and knee exercises already referred to also depends to a large extent on the coöperation of the patient.

By this method it should be possible to obtain accurate reduction and firm union in almost all fractures of this area of the shaft of the femur. Open operation on such a fracture should be regarded as a confession of failure. The total cost of the apparatus required works out at about £8 a bed; this should be well within the means of any hospital. To keep the patient in bed until union is firm enough to begin weight-bearing may seem to occupy a hospital bed longer than is absolutely necessary; but only too often, as in the cases already mentioned, an attempt to mobilise a patient, before union is quite firm, by the use of a walking calliper, plaster, or other means consumes more time in the long run. In conclusion I emphasise that any attempt at an "easy way" or "short cut" in the treatment of a fracture of the shaft of the femur is a snare and a delusion.

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VITAMINS D_2 AND D_3 AND A.T. 10

IN CONGENITAL THYROID AND PARATHYROID DEFICIENCY

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THE patient on whom these investigations were made first came under the care of the Medical Unit, University College Hospital, in January, 1934, when he was 13, and he has continued under regular observation since. This long period of observation provided the opportunity to assess the value of several different therapeutic substances which have been used in the treatment of parathyroid deficiency. The patient proved to be unusually suitable in that his clinical and biochemical reactions to forms of treatment remained constant and easily reproducible, so that conclusions regarding the relative potency of the different therapeutic substances tested, for this particular case, could be made with some degree of confidence. A preliminary report of the case was made by Elliott (1935).

The boy was the only child of healthy parents. He was delivered at full term by cæsarean section. Growth was retarded, and for this reason he was occasionally given thyroid extract. When he was 5, major and minor epileptic fits began, and in 1933, when he was 12, he came under the care of Dr. E. A. Blake Pritchard for this condition (Pritchard 1934). At this time cataracts in both eyes and tetany suggested the correct diagnosis. In 1934 he was admitted to University College Hospital. He was a sturdy youngster with a mop of violent red hair. His height was 4 ft. 5 in. and his weight 5 st. 11 lb. The cataracts in both eyes had developed only to the stage of impairing vision. The mental development was incommensurate with his years. He could answer simple questions but could neither count nor spell. The thyroid could not be felt in the neck, and hard irregular deposits about the size of a bean were found round the tendons of the knee-joints. Radiography showed that these deposits were calcareous. No evidence of disease of the skeletal bones was found. Chvostek's and Trousseau's signs were positive, and the electrical reactions of the nerves were increased. His fits were of two kinds: typical carpopedal and laryngeal spasms, and equally typical major epilepsy occurring independently. The blood-calcium and plasma inorganic phosphate have been estimated about every month since January, 1934, always in the same laboratory and by or under the supervision of one of us (M. M.). Calcium-balance experiments were not made. Ordinary diet was allowed and no attempt made to limit the intake of phosphates. A pint of milk was usually taken every day.

THYROID DEFICIENCY

When the patient first came under observation, his basal metabolic rate (B.M.R.) was − 25 per cent. At this time his serum calcium was 5 mg. per 100 c.cm. and the plasma inorganic phosphate 9·0 mg. per 100 c.cm. When the parathyroid deficiency was treated, the serum calcium rose to 9·4 mg. and the plasma phosphate fell to 5·6 mg. At this time the B.M.R. still remained low, at − 18 per cent. Thyroid siccum gr. 1½ daily was then given, and the B.M.R. rose to + 10 per cent. This dose of thyroid extract has been continued ever since, and the B.M.R. has remained normal despite subsequent lapses into calcium deficiency and tetany. Today the boy looks strong and can walk ten miles. His early thyroid deficiency has left him mentally backward, but he can now do simple work in a shop. It appears that the thyroid deficiency is functionally independent of, and exerts no influence on, the parathyroid deficiency.

FITS

With remarkable constancy the signs of tetany disappeared when the boy's blood-calcium rose above 7 mg. per 100 c.cm. and reappeared when the blood-calcium fell below this figure. The epileptiform attacks similarly disappeared when the blood-calcium rose, and they never reappeared except when the blood-calcium was deliberately allowed to fall to a level below 5·5 mg. per 100 c.cm.

TREATMENT

The first year of treatment was occupied in determining the form of therapy which would stabilise the patient. In this period the cataracts were successfully removed by Mr. Humphrey Neame. The effect of parathyroid extracts was first tried. Euparatone was given first in doses of 10 units daily for a week and then in doses of 20 units daily for ten days; it did not affect either the symptoms or the blood-calcium. One injection of 100 units of Parathormone was then given; this raised the blood-calcium from 4·8 mg. to 6·8 mg. per 100 c.cm. The patient then left hospital but returned at the end of May to receive a course of the German product A.T. 10 (dihydrotachysterol) by mouth.

On readmission the patient's blood-calcium was 5·1 mg. per 100 c.cm. Over the next two months he received doses of A.T. 10 up to 5 c.cm. twice a week, and under this treatment the blood-calcium rose to 9·6 mg. and the plasma phosphate fell to 5·6 mg. Thereafter the patient received a solution of Calciferol (vitamin D_2) in oil, finally receiving for a fortnight 1,500,000 international units daily. Treatment was then stopped, the blood-calcium having risen to 12·2 mg., while the phosphate had fallen to 3·6 mg. This huge supply of calciferol was apparently stored to some extent, for with no further treatment the blood-calcium remained steady for three months at about 9 mg. and thereafter slowly fell until, after a further five months without treatment, mild symptoms of tetany reappeared, the blood-calcium then being 6·7 mg. and the plasma phosphate 7·2 mg. Treatment was resumed a month later, and ultimately the boy was stabilised on a dose of 500,000 I.U. of vitamin D_2 weekly, given by mouth in oily solution with milk,

half the dose on the third, and half on the seventh, day of the week. This dosage did not seem to lead to storage, for withdrawal was followed in two or three weeks by a fall in the calcium. For four long periods—the first two periods each of one year's duration, the third of four months, and the fourth which has continued since May, 1939—the boy has received this dosage of vitamin D_3. Throughout each period the blood-calcium has oscillated within narrow limits round 8 mg., but the plasma phosphate has varied more widely, most of the monthly estimations being 3–5 mg. but occasionally reaching 6 mg. per 100 c.cm. Despite this continued high dosage the patient has at no time shown any of the symptoms ascribed to overdosage of vitamin D (see Wyatt, Hicks, and Thompson 1936–37), nor does he show in either arteries or kidneys any signs of metastatic calcification. The absence of abnormal calcification, apart from the unchanged calcareous deposits round the knees, is probably to be ascribed to the fact that in him, unlike normal subjects, the large dose of calciferol did not produce hypercalcæmia; if so, this supports the view that the signs associated with excessive dosage of vitamin D are to be attributed not to the effect of the vitamin but to the concomitant production of hypercalcæmia.

COMPARISON OF VITAMIN D_2 AND A.T. 10

After a preliminary period of ten months' stabilisation on 500,000 I.U. of vitamin D_2 weekly the patient was given A.T. 10 for ten months, and then for a further period of twelve months he returned to his weekly dosage of 500,000 I.U. vitamin of D_2. The estimations of the blood-calcium and the plasma phosphate are summarised in the accompanying table, which shows that administration of A.T. 10 prevented the blood-calcium from falling to the low levels found before any treatment was given, and to this extent the preparation was effective. This

COMPARISON OF VITAMIN D_2 AND A.T. 10

Substance	Weekly dose	Test period	Blood-calcium (mg. per 100 c.cm.)			Plasma phosphate (mg. per 100 c.cm.)		
			Obsv.	Mean	S.D.	Obsv.	Mean	S.D.
Vit. D_2	5×10^5 units	Aug., 1935–May, 1936	11	8·0	0·70	7	6·0	0·92
A.T. 10	1–6 c.cm.	June, 1936–March, 1937	12	7·1	0·94	12	3·8	1·02
Vit. D_2	5×10^5 units	April, 1937–March, 1938	10	8·4	0·61	10	3·2	0·87

Obsv. = Number of observations.
S.D. = Standard deviation of series.

effect, however, was only achieved by steadily increasing the dosage of A.T. 10. For three months 1 c.cm. a week appeared to be sufficient, but later this dose had to be increased, until finally the patient was receiving 6 c.cm. a week. Further, the blood-calcium levels varied erratically, and the frequency with which the Chvostek sign was positive indicated that the patient was on the verge of full tetany. The impression gained from the comparison of A.T. 10 with vitamin D_2 was that in this patient vitamin D_2 produced a more stable state than did A.T. 10. The reason for the high values for plasma phosphate in the preliminary period of treatment with vitamin D_2 is unknown.

VITAMIN D_2 AND VITAMIN D_3

After the period from March, 1937, to March, 1938, when the patient was receiving 500,000 I.U. of vitamin D_2 weekly and the blood-calcium averaged 8·4 mg. per 100 c.cm. and the plasma phosphate 3·2 mg. per 100 c.cm., the effect of vitamin D_3 was tested. Over a period of a month 250,000 I.U. weekly of vitamin D_3 were given. The blood-calcium fell to 6·8 mg. with a plasma phosphate of 4·7 mg. per 100 c.cm. The dose was then increased to 500,000 I.U. of vitamin D_3 weekly, and this dose was continued for two and a half months. The blood-calcium rapidly rose and remained round 8·8 mg., while the plasma phosphate fell to 3·2 mg. Thereafter for a period of four and a half months the patient returned to his original dosage of 500,000 I.U. vitamin of D_2 weekly, and during this period the blood-calcium and plasma phosphate remained at their usual levels. The action of vitamin D_3 therefore seemed to be identical in this patient with the action of vitamin D_2.

VITAMIN D_3 AND OSTELIN HIGH-POTENCY TABLETS

After the last period of treatment with vitamin D_3 the effect of Ostelin high-potency tablets was tried. Each tablet contained 50,000 I.U. of the same preparation of vitamin D_2 provided by the same firm, and the dosage of 10 tablets was distributed over the week. Soon after the start of this treatment the patient's blood-calcium began to fall. In view of the possibility that this might be attributable to retardation of absorption from the gut owing to the hard coating of sugar, the tablets were taken crushed in milk. Despite this the level of blood-calcium fell progressively to 6·6 mg., the plasma phosphates rising to 5 mg. The dosage was then increased from 500,000 to 800,000 I.U. a week, and although the blood-calcium rose and the blood-phosphate fell a little, they did not reach the levels which were produced and maintained when the weekly dosage of 500,000 I.U. of vitamin D_2 in oil was resumed. It appears that, either because of difficulty of absorption or perhaps through deterioration of the vitamin D_2 contained, the Ostelin concentrated tablets were not so effective as the same dose of vitamin D_2 dissolved in oil.

SUMMARY

(1) A case of congenital thyroid and parathyroid deficiency associated with tetany and epilepsy is described.

(2) Successful treatment of the tetany had no effect on the symptoms of thyroid deficiency, nor did treatment of the thyroid deficiency alone influence the development of tetany. The tetany was therefore independent of the thyroid deficiency with its partial cretinism.

(3) When the blood-calcium rose above 7 mg. per 100 c.cm., the epileptic fits and tetany disappeared. When the blood-calcium fell below this level, tetany and epileptic fits reappeared.

(4) The parathyroid deficiency was controlled by the oral administration of vitamin D_3 (calciferol) in oil, 500,000 units weekly. Despite the continued administration of this large dosage of vitamin D_3 or comparable dosages of related substances, for nearly six years no signs of hypervitaminosis D have appeared.

(5) The German preparation A.T. 10 was effective in controlling the parathyroid deficiency, but it appeared less reliable in its action than vitamin D_3.

(6) Vitamin D_3 was simply equivalent to vitamin D_2 in controlling the parathyroid deficiency.

During most of these investigations the patient was at University College Hospital under the care of Prof. T. R. Elliott, whom we thank for permission to publish his records. We also thank Prof. E. Holz, of the Charité Hospital, Berlin, for supplying the preparation A.T. 10; to Dr. A. L. Bacharach, of the Glaxo laboratories, for the calciferol in oil and the ostelin tablets; and Sir Henry Dale for the supply of vitamin D_3.

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POTENCY OF VITAMINS D_2 AND D_3

IN OSTEOMALACIA AND LATE RICKETS

BY DAGMAR CURJEL WILSON, M.D. Glasg., M.R.C.P., M.R.C.O.G., D.P.H.

THE relative values of vitamin D_2 or calciferol from irradiated ergosterol and of vitamin D_3 from irradiated 7-dehydrocholesterol, in which form vitamin D is present in cod-liver oil, in the treatment of human rickets are of considerable importance. The antirachitic potency of vitamin D_3 in rats is 40,000 I.U. per mg., and that of vitamin D_3 is about the same (Schenck 1937). In chickens vitamin D_3 has a relatively much greater antirachitic activity than vitamin D_2—sixty times greater, weight for weight (Brockmann 1938). As regards the treatment of infantile rickets, there are conflicting reports of the relative activities of vitamins D_2 and D_3, given either as the pure substance or in cod-liver oil or fish-liver oils. The evidence has been reviewed by Morris and Stephenson (1939), who found no detectable difference in the relative potencies of pure vitamins D_2 and D_3 in infantile rickets.

EXPERIMENTS

Our samples of vitamins D_2 and D_3, supplied by Sir Henry Dale, were similar to those tested on rats and found to have equal antirachitic potencies in an experiment carried out by nine laboratories in collaboration and organised by the vitamin-D subcommittee of the Accessory Food Factors Committee. The results of this test are being published by Coward (1940). Our samples of vitamins D_2 and D_3 were also similar to those used by Morris and Stephenson (1939), and to those used by Himsworth and Maizels in their work described elsewhere in this issue.

The patients chosen for treatment were Indians living in the Kangra valley, Punjab, where rickets and osteomalacia affect, at all ages and in both sexes, a community which lives an out-of-door life. My previous experience (Wilson 1929) led me to classify the patients before treatment into three grades, +, ++, +++, according to the severity of their symptoms. Since radiography was not available, this classification had to be based on clinical signs of present activity of the disease; for osteomalacia these included pain, muscular spasm and difficulty in walking rather than deformity of pelvic and other bones which might be long-standing and incurable. The criteria in the diagnosis of late rickets were slightly different and included enlarged epiphyses and stunted growth. In assessing the value of treatment attention was paid to subjective symptoms, including pain in the lumbrosacral region, pelvic girdle, legs, ribs, shoulder girdle, and arms; flexor (carpopedal) spasm was also taken into account. The patients were chiefly females aged 20–40, but a few males were included, and the total range of the ages was 6–70. For the therapeutic trials patients with osteomalacia or with late rickets of similar grades of severity were grouped into pairs; pure vitamin D_2 was given to one of each pair and pure vitamin D_3 in the same dosage to the other. The deformity and pain before treatment and the improvement after treatment were assessed independently by members of the staff of the Canadian Mission Hospitals in the Kangra valley, who have a wide experience of rickets. The patients were examined weekly, and the degree of improvement in the flexor spasm and pains was classified as none, slight, definite, good, or cured.

The samples of pure crystalline vitamins D_2 and D_3, prepared by Mr. T. A. Webster of the National Institute of Medical Research, Hampstead, were dissolved in olive oil so that the solutions contained 5250 I.U. of the vitamin per c.cm. as calculated from the biological tests on rats (Coward 1940). The solutions were stored in dark glass bottles in a cold place and protected from light. The clinical tests were carried out in the winter season between autumn, 1938, and spring, 1939. One large dose of either vitamin was given once a week. For convenience and accuracy of administration the dose was put directly into the patient's mouth from the barrel of a graduated hypodermic syringe. The observations were made on thirteen pairs of patients with osteomalacia and two pairs with late rickets, and treatment was continued for three or four weeks. The dose given to both members of a pair was either 10,500 or 21,000 I.U. of vitamin D weekly, and the total amount given over the whole period of treatment varied from 21,000 to 84,000 I.U.

TABLE I—RESULTS OF TREATMENT OF OSTEOMALACIA AND OF LATE RICKETS WITH WEEKLY DOSES OF 10,500 OR OF 21,000 I.U. OF VITAMIN D

No. and description of case	Degree of severity before treatment	Total dosage (I.U.)	Duration of treatment (weeks)	Improvement	Vitamin found superior
31 OM	+ + +	84,000	4	D_3 definite	D_3
32 ,,	+ + +	,,	,,	D_2 good	
27 OM	+ + +	,,	,,	D_3 definite	Neither
28 ,,	+ + +	,,	,,	D_2 ,,	
25 OM	+ + +	42,000	2	D_3 ,,	,,
26 ,,	+ + +	,,	,,	D_2 ,,	
1 OM	+ + +	52,500	4	D_3 good	,,
2 ,,	+ + +	,,	,,	D_2 ,,	
3 OM	+ + +	,,	,,	D_3 cured	D_3
4 ,,	+ + +	,,	,,	D_2 good	
5 OM	+ + +	,,	,,	D_3 definite	D_3
6 ,,	+ + +	,,	,,	D_2 cured	
7 OM	+ + +	42,000	,,	D_3 slight	,,
8 ,,	+ + +	,,	,,	D_2 definite	
9 OM	+ + +	,,	,,	D_3 good	Neither
10 ,,	+ + +	,,	,,	D_2 ,,	
11 OM	+ + +	31,500	2	D_3 ,,	D_3
12 ,,	+ + +	,,	,,	D_2 definite	
13 OM	+ + +	21,000	,,	D_3 cured	,,
14 ,,	+ + +	,,	,,	D_2 definite	
15 OM	+ + +	42,000	4	D_3 good	,,
16 ,,	+ + +	,,	,,	D_2 definite	
21 OM	+ + +	,,	,,	D_3 ,,	D_3
22 ,,	+ + +	,,	,,	D_2 good	
29 OM	+ + +	,,	2	D_3 cured	D_3
30 ,,	+ + +	,,	,,	D_2 almost cured	
17 LR	+ +	52,500	4	D_3 definite	D_3
18 ,,	+ +	,,	,,	D_2 good	
19 LR	+ +	31,500	,,	D_3 ,,	,,
20 ,,	+ +	,,	,,	D_2 cured	

OM = Osteomalacia; LR = Late rickets.

RESULTS

To make a quantitative comparison it is essential to ascertain the minimal curative dose of each substance. With a weekly single dose of 10,500 I.U. of either vitamin progress was extremely slow, and the patients, noticing little improvement in their symptoms after two such weekly doses, became restive and unwilling to have further treatment. Improvement followed subsequent treatment with a weekly single dose of 21,000 I.U. Of the fifteen pairs of patients, five pairs were treated with 10,500 I.U. from the start and observed for two or three weeks before the dose was increased (see table II). Another group of four pairs received 21,000 I.U. from the start and were observed for a similar period (table III). The results obtained in these nine pairs, after increase of dosage in some cases, and in the remaining six pairs, most of whom received 10,500 I.U. once and 21,000 I.U. subsequently, are shown in table I, with the total dosage and full period of treatment.

Tables I and III seem to indicate that there was no difference in the clinical effectiveness of the two forms of the vitamin. The results obtained in the five pairs treated with minimal dose (table II) and therefore the most important show, however, vitamin D_2 as the more active in one case and vitamin D_3 as the more active in three cases, while the two vitamins appear equal in one case. It is a pity that there are not more than five of these crucial pairs of cases, because, in view of the small number of cases, the smallness of the difference to be assessed and the subjective nature of the assessment, the result cannot be regarded as significant of any difference in potency between vitamins D_2 and D_3.

TABLE II—RESULTS OF TREATMENT OF OSTEOMALACIA AND OF LATE RICKETS WITH WEEKLY DOSES OF 10,500 I.U. OF VITAMIN D

No. and description of case	Vitamin given	Improvement after			Vitamin found superior
		1 week	2 weeks	3 weeks	
7 OM	D_2	None	None	Not examined	D_3
8 ,,	D_3	Slight	Slight		
9 OM	D_2	None	Definite	,,	Neither
10 ,,	D_3	,,	,,	,,	
13 OM	D_2	Slight	Cured	,,	D_2
14 ,,	D_3	None	Definite	,,	
21 OM	D_2	,,	Slight	,,	D_2
22 ,,	D_3	Slight	Definite	,,	
19 LR	D_2	None	Slight	Definite	D_2
20 ,,	D_3	Slight	Cured	Cured	

An additional pair of patients with late rickets is not included in the above. Two boys, about 11, were admitted to a hospital where radiography was available. One of them received each week 21,000 I.U. of vitamin D_2 and the other a similar dose of vitamin D_3. In both boys increased density of bone was observed at the end of three weeks.

No ill effects from the method of dosage were observed, and the weekly spacing was convenient and popular with both patients and staff. In comparison with the degree of cure previously effected in treating similar cases (Wilson 1931) with a total vitamin dosage approximately the same but administered daily as cod-liver oil or as irradiated ergosterol, the use of spaced large doses was considered to shorten the treatment by at least two weeks. Bischoff and Brieger (1938) also found that, in early rickets and spasmophilia, the signs of cure were evident several days earlier with the one large dose of vitamin D_3 or of vitamin D_2 than with the same amount of vitamin given in smaller daily doses.

TABLE III—RESULTS OF TREATMENT OF OSTEOMALACIV WITH WEEKLY DOSES OF 21,000 I.U. OF VITAMIN D

Case	Vitamin given	Improvement after		Vitamin found superior
		1 week	2 weeks	
31	D_2	None	None	D_2
32	D_3	Slight	Definite	
27	D_2	,,	,,	Neither
28	D_3	,,	,,	
25	D_2	,,	,,	,,
26	D_3	,,	,,	
29	D_2	Definite	Cured	D_2
30	D_3	,,	Almost cured	

SUMMARY

(1) The therapeutic effects of pure specimens of vitamin D_2 from irradiated ergosterol and of vitamin D_3 from irradiated 7-dehydrocholesterol were compared in thirteen pairs of patients with osteomalacia and in two pairs with late rickets among Indians, aged 6–70, in the Kangra valley, Punjab.

(2) The results, assessed by clinical estimates of the patient's progress and by the disappearance of carpopedal spasm, of pain in specified sites, and of difficulty in walking, showed the two preparations to be equally effective. For both preparations a dose of 10,500 I.U. of vitamin D weekly caused only slow improvement within a period of two weeks, whereas a dose of 21,000 I.U. caused improvement in a week.

(3) The advantages of spaced weekly doses are indicated.

This investigation was made possible by a grant from the Royal Society. I am indebted to Sir Henry Dale for the preparations of vitamins D_2 and D_3; to Dr. W. R. Aykroyd and the Indian Research Fund Association for the assistance of Dr. K. L. Shourie in the Kangra valley; the Canadian Mission for their hospital facilities; and Major G. Taylor, I.M.S., for looking after the two Kangra boys whose treatment was controlled by radiography at the Mayo Hospital, Lahore.

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ZINC PROTAMINE INSULIN AND SOLUBLE INSULIN

INTERACTION IN COMBINED DOSES

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THE introduction of the slower-acting insulins has made it possible to balance the metabolism of many diabetic patients on one injection of insulin a day consisting of enough soluble or ordinary insulin (S.I.) to promote the utilisation of food eaten at breakfast, drawn into the same syringe with an equal or larger amount of zinc protamine insulin (Z.P.I.) which comes into play later in the day for the other meals. In practice this usually works well, and the total quantity of insulin needed to keep the blood-sugar within normal limits during the day is less than when two doses of soluble insulin are used. Case 2 (fig. 1 and table I) shows typical estimations of the blood-sugar throughout the day, where S.I. 50 U. in the morning and 38 U. in the evening produced a fluctuating curve, whereas a combined dose of Z.P.I. 40 U. with S.I. 38 U. kept the blood-sugar within normal limits. The total quantity of insulin can be still further reduced if the doses of S.I. and Z.P.I. are given in separate injections, one immediately after the other, instead of being drawn into the same syringe and injected together.

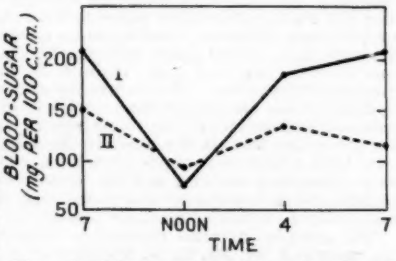

FIG. 1.—Blood-sugar values in case 2 (see table I): (I) S.I. 50 U. given at 7.15 A.M. and 38 U. at 6.45 P.M.; (II) Z.P.I. 40 U. and S.I. 38 U. given at 7.15. A.M.

Attention was drawn to this point by an active diabetic (case 12), who for several months had given himself one injection containing Z.P.I. 20 U. with S.I. 16 U. half an hour before breakfast every morning; he changed the method one day and gave the two kinds of insulin in separate injections. He had an attack of hypoglycæmia before luncheon. He has continued the separate injections and has reduced the S.I. to 8 U., the Z.P.I. remaining the same. Fig. 2 and table I, case 12, show better control of the blood-sugar throughout the day after Z.P.I. 20 U. and S.I. 8 U. given in separate injections than after Z.P.I. 20 U. with S.I. 16 U. in the same syringe.

EXPERIMENTS AND RESULTS

Z.P.I. is ordinary S.I. with a minute quantity of zinc combined in a firm suspension with protamine, which delays the absorption from the tissues and thus retards the hypoglycæmic action. It therefore seems reasonable to suppose that this suspension may also delay the absorption of S.I., if mixed with it before injection, and perhaps convert it in effect into Z.P.I. This supposition was tested in the following way:—

Seventeen hospital patients, women over middle age, who were being balanced on a combined dose of the two kinds of insulin, had a blood-sugar curve

TABLE I—BLOOD-SUGAR IN TYPICAL CASES

Case 2	Fig. 1, I							Fig. 1, II					
	Time							Time					
	A.M.		Noon	P.M.				A.M.		Noon	P.M.		
	7.0	7.15		4.0	6.45	7.0	11.0	7.0	7.15		4.0	7.0	11.0
Blood-sugar (mg. per 100 c.cm.) ..	206	—	75	200	—	215	—	150	—	93	131	118	—
Insulin (units) ..	—	S.I. 50	—	—	S.I. 38	—	—	—	Z.P.I. 40 S.I. 38	—	—	—	—

Case 12	Fig. 2, I							Fig. 2, II					
Blood-sugar (mg. per 100 c.cm.) ..	100	—	112	281	—	168	68	81	—	118	175	137	231
Insulin (units) ..	—	Z.P.I. 20 S.I. 16 together	—	—	—	—	—	—	Z.P.I. 20 S.I. 8 separately	—	—	—	—

Case 4	Fig. 3, I									Fig. 3, II								
	Fasting	Br.	Half-hour intervals							Fasting	Br.	Half-hour intervals						
			2	3	4	5	6	7	8			2	3	4	5	6	7	8
Blood-sugar (mg. per 100 c.cm.) ..	162		212	225	225	200	231	212	175	137		200	212	212	193	187	137	62
Insulin (units) ..	Z.P.I. 22 S.I. 22 together		—	—	—	—	—	—	—	Z.P.I. 22 S.I. 22 separately		—	—	—	—	—	—	—

Case 18	Fig. 4, I									Fig. 4, II								
Blood-sugar (mg. per 100 c.cm.) ..	225	Br.	262	250	418	225	250	237	237	193	Br.	225	231	243	225	231	225	193
Insulin (units) ..	Z.P.I. 60 S.I. 40 together		—	—	—	—	—	—	—	Z.P.I. 60 S.I. 40 separately		—	—	—	—	—	—	—

Case 12	Fig. 5, I									Fig. 5, II								
Blood-sugar (mg. per 100 c.cm.) ..	100	Br.	112	124	224	162	206	156	131	93	Br.	312	337	510	418	281	281	256
Insulin (units) ..	Z.P.I. 20 S.I. 8 separately		—	—	—	—	—	—	—	Z.P.I. 20 S.I. 8 together, not mixed		—	—	—	—	—	—	—
	Fig. 5, III									Fig. 5, IV								
Blood-sugar (mg. per 100 c.cm.) ..	168	Br.	250	374	424	468	518	424	393	87	Br.	156	268	312	398	418	412	368
Insulin (units) ..	Z.P.I. 20 S.I. 8 together well mixed		—	—	—	—	—	—	—	Z.P.I. 20 alone		—	—	—	—	—	—	—
	Fig. 5, V																	
Blood-sugar (mg. per 100 c.cm.) ..	218	Br.	225	281	293	268	237	218	143									
Insulin (units) ..	Z.P.I. 20 S.I. 16 together		—	—	—	—	—	—	—									

Z.P.I., zinc protamine insulin.
S.I., soluble or ordinary insulin.
Br., breakfast.

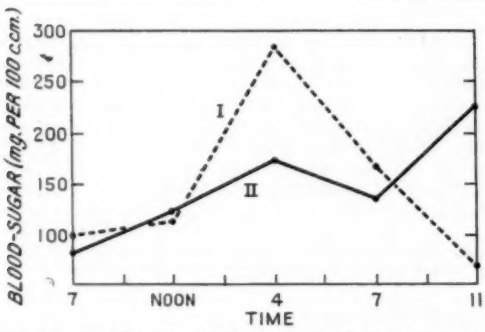

FIG. 2.—Blood-sugar values in case 12 (see table I): (I) Z.P.I. 20 U. and S.I. 16 given together at 7.15 A.M.; (II) Z.P.I. 20 U. and S.I. 8 U. given separately at 7.15 A.M.

estimated on two different days: on the first the Z.P.I. and S.I. were given in the same syringe as usual; on the second day they were given separately. The diet was constant and contained about 180 g. of carbohydrate. The fasting blood-sugar was estimated; insulin was injected forthwith and followed in half an hour by breakfast; and post-insulin estimations were begun an hour after the injection and continued half-hourly till four hours had elapsed.

The results show that, when the injections were given separately, the S.I. had the expected effect of bringing the blood-sugar to near the fasting level at the end of four hours. In twelve cases it was below the fasting level, five being hypoglycæmic; in one case the fasting and end points were the same; and of the remaining four the highest end point was 156 mg. per 100 c.cm. When, however, the same doses of insulin were mixed, the result was different; the end point was higher than the fasting level in twelve cases, equal in two, and, although lower in the remaining three, had risen to over 300 mg. per 100 c.cm. during the four-hour period in two of these cases, while in the third there was hypoglycæmia when the injections were given separately. Moreover, the shape of the curve was altered when the dose was combined, in all the cases except one and fell into one of three groups, of which case 4 (fig. 3) and case 18 (fig. 4) show typical forms. The findings on which the graphs are based are given in table I. The first type occurred in one case only. The post-insulin estimations ran in almost straight lines parallel to each other; there was no normal rise or fall, the greatest fluctuation being from 110 to 118 mg. per 100 c.cm. The patient was obese, receiving only 16 units of insulin (Z.P.I. 10 U. and S.I. 6 U.) and was probably insensitive to insulin. The second type of curve, after following a normal course for two or three hours, rose or ceased to fall towards the end (fig. 3). Six cases were in this group, in two of which there was hypoglycæmia after the first one and a half hours when the injections were given separately. In the third and commonest post-insulin graph (ten cases) there was a remarkable peak where the blood-sugar rose suddenly and usually fell in half an hour to the former level (fig. 4). There was apparently a short escape from insulin control, which was pronounced in seven cases and slight and more gradual in three. In all the cases the S.I. was more active, and less was needed when separate injections were used.

Case 12 presents a contrast to the hospital cases; the subject had been taking insulin for fourteen years and was doing full work in an active profession; at the time of the experiment he was receiving separate injections of Z.P.I. 20 U. and S.I. 8 U. every morning, whereas the other patients had been recently balanced on insulin and were receiving the combined dose until the second day of the investigation. Five experiments were made in case 12 to find out whether the degree of mixing in the syringe affects the action of the S.I., and whether, if a large proportion of S.I. is given, some of it escapes and performs its normal action. In the first test the separate injections were continued, the resulting curve (fig. 5, I) being approximately normal. Secondly, the patient drew the two kinds of insulin into the same syringe, taking the heavier Z.P.I. first and trying not to mix them. The curve (fig. 5, II) was of the "escape" type but rose much higher than in any of the hospital cases—to 510 mg. per 100 c.cm.—and did not fall so suddenly; it had reached 250 mg. per 100 c.cm. at the end of four hours. In the third experiment the two insulins were deliberately mixed; the blood-sugar soared to 518 mg. per 100 c.cm., though rather more slowly; it was falling very slowly, having only reached 393 mg. per 100 c.cm. at the end of four hours (fig. 5, III). It is rather in the slow fall than in the height of the maximal point that this curve shows less insulin control than the last and in this respect the mixing diminished the

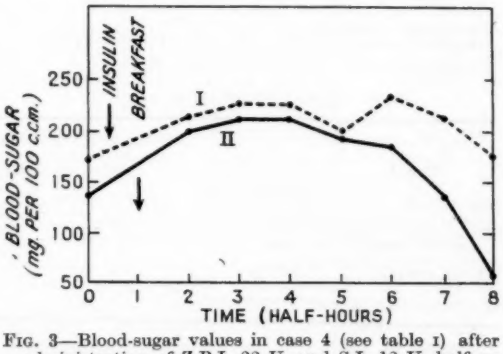

FIG. 3—Blood-sugar values in case 4 (see table I) after administration of Z.P.I. 22 U. and S.I. 12 U. half an hour before breakfast: (I) together; (II) separately.

action of the S.I. Lastly, the patient took Z.P.I. 20 U. alone, omitting the S.I. altogether. The curve (fig. 5, IV) is almost parallel to the previous curve (fig. 5, III), starting lower and not rising so high, but it shows even less fall.

The action of the S.I. may be assessed in two ways in these curves: (1) the difference between the maximal height and the end point, which shows the extent of the hypoglycæmic action; and (2) the difference between the fasting point and the end point, which should be nil if the insulin is sufficient; the nearer they approximate the better the action of the S.I. These figures are shown in table II. It is evident that the mixing of the two insulins in the syringe diminished the action of the S.I. but did not abolish it altogether.

The proportion of S.I. to Z.P.I. was greater in the hospital cases than in case 12, where it was 4 to 10. In two cases it was 5 to 10 and ranged upwards to 10 to 10. Although in case 12 the S.I. 8 U. given in the same syringe with Z.P.I. exerted some effect on the post-insulin curve, the escape from insulin control was greatly exaggerated compared with even the worst of the hospital cases, and the curves provide a remarkable contrast to the one which shows the effect of the same

insulin given separately. It seemed therefore probable that in the hospital cases there was enough S.I. for some to escape and to act within the first four hours, whereas in case 12 there was not. To test this hypothesis a fifth curve was estimated in case 12 after injecting a double dose (16 U.) of S.I. from the same syringe with the original amount, 20 U. of Z.P.I. Fig. 5, v, shows that the end point was well below the

TABLE II—CASE 12

BLOOD-SUGAR DIFFERENCES (MG. PER 100 C.CM.)

Insulin (units)	How given	Maximum to end point	End point to fasting point
Z.P.I. 20 S.I. 8	Not mixed	254	163
Z.P.I. 20 S.I. 8	Mixed	125	225
Z.P.I. 20 S.I.0	Alone	50	281

fasting level, and that enough of the S.I. did escape to exert a strong hypoglycæmic action. This curve is a great contrast to Fig. 5, II and III, where only 8 U. of S.I. was used. The larger proportion of S.I. needed in the hospital cases is therefore due to the combined method of administration, and it is probable that with this method more S.I. will always be needed.

The next question that arose was more difficult to answer. What happens to that part of the S.I. which does not act within the first four hours? Does it act late in the day? Estimations of the blood-sugar were made at 7 P.M., twelve hours after the injection of the insulin in three hospital cases on the two days of the experiment. Table III shows the blood-sugar at noon and at 7 P.M. It will be observed that when the insulins were given together the 7 P.M. estimation was always lower than when the injections were separate, whereas at noon the blood-sugar was lower after separate injection in each case. Fig. 2 shows similar fluctuations in case 12. Twice the amount of S.I. was given when the insulins were combined. The blood-sugar reached a hypoglycæmic level at 11 P.M., whereas with separate injections it was highest at this time. On the day of the combined injection the subject ate about 20 g. of carbohydrate after the 11 P.M. estimation; the blood-sugar was 125 mg. per 100 c.cm. at 7 A.M. the next day, but hypoglycæmic symptoms developed at noon. This evidence suggests that the action of

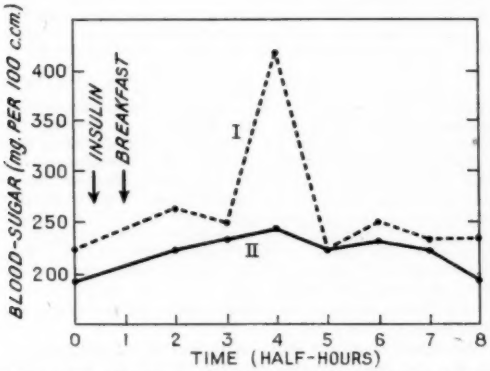

FIG. 4—Blood-sugar values in case 18 (see table I) after administration of Z.P.I. 60 U. and S.I. 40 U. half an hour before breakfast: (I) together; (II) separately.

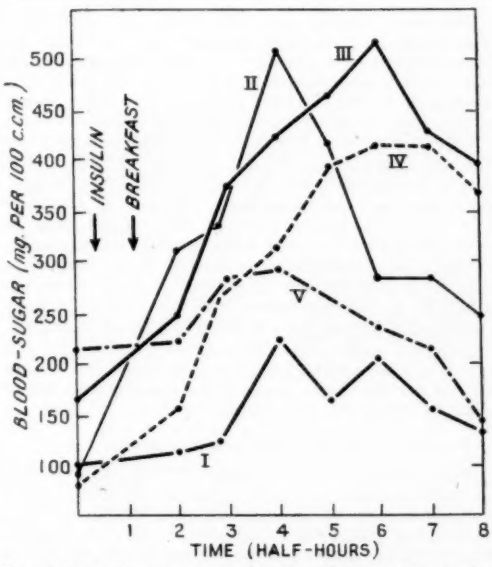

FIG. 5—Blood-sugar values in case 12 (see table I) after insulin given half an hour before breakfast: (I) Z.P.I. 20 U. and S.I. 8 U. separately; (II) same doses together but not mixed; (III) same doses together and well mixed; (IV) Z.P.I. 20 U. alone; (V) Z.P.I. 20 U. and S.I. 16 U. together.

part of the S.I. is delayed, acting later in the day and even into the next day. It also seems that part of the S.I. is lost. In case 12, for instance, less total insulin is needed when the injections are given separately, and the patients who became hypoglycæmic within four hours of the separate injections did not become hypoglycæmic later in the day or the next day when the combined injections were continued.

TABLE III—BLOOD-SUGAR (MG. PER 100 C.CM.) AT NOON AND 7 P.M.

Case no.	Insulin (units)	7 A.M.	Noon	7 P.M.
15	Z.P.I. 18 Together	75	87	131
	S.I. 24 Separately	68	43	231
17	Z.P.I. 24 Together	93	193	93
	S.I. 20 Separately	93	175	231
18	Z.P.I. 60 Together	225	231	137
	S.I. 40 Separately	193	193	218

DISCUSSION

It is clear that the process of drawing S.I. into the same syringe with Z.P.I. altered its action to some extent in all these cases and made it less effective during the four hours after injection. Three details in administration seemed to be important: the degree of mixing; the relative proportions of Z.P.I. and S.I.; and the total quantity of insulin.

Degree of mixing.—For instance, in fig. 5, II, where mixing was avoided so far as possible, the blood-sugar fell sooner and farther than in fig. 5, III, where mixing was deliberate. There is less mixing if the heavier Z.P.I. is drawn into the syringe first; the lighter S.I. remains floating on the top until the moment of inverting the syringe to thrust the needle through the skin. It is essential to avoid injecting even a minute particle of the Z.P.I. already in the syringe, into the bottle containing S.I.

Relative proportions of Z.P.I. and S.I.—The more S.I. there is, the more escapes and produces its typical effect—e.g., in case 12 twice the usual quantity of S.I. was needed when given as a combined dose, and all the hospital patients were given a dose of S.I. equal to a half or more of the Z.P.I.

The total quantity of insulin must also be considered because if part of the S.I. is converted into the slower acting insulin this will accumulate and continue to act longer and longer as time goes on. In the cases with the escape type of curve we may suppose that the previous day's Z.P.I. continued to act at the beginning of the experimental period, leaving a gap before the delayed S.I. came into play. In case 12 there was probably no accumulation, the Z.P.I. 20 U. taken alone being just enough to keep the blood-sugar low during the night, with none to carry over till the next day; but, when the patient doubled the dose of S.I., some did carry over and cause symptoms of hypoglycæmia the next day.

SUMMARY AND CONCLUSIONS

Two post-insulin blood-sugar curves of seventeen hospital diabetic patients recently balanced on a combined dose of zinc protamine insulin (Z.P.I.) and soluble insulin (S.I.) and five of a long-standing diabetic in full activity were plotted, one in each case being estimated after separate injections and the others after the two kinds of insulin had been mixed in the syringe.

When the two insulins were drawn into the same syringe, the action of the S.I. was modified, some of it being delayed in action and some of it apparently lost; in all cases a larger proportion of S.I. was needed when given in the same syringe with Z.P.I. to produce a hypoglycæmic action in the early part of the day.

It seems from this investigation that it is more economical and ensures more accurate balancing to give S.I. and Z.P.I. in separate injections. If drawn into one syringe they must not be allowed to mix.

The hardened diabetic does not mind two pricks, and all who lead active lives prefer to take all their insulin in the morning, rather than have to remember a second injection before tea or before dinner; hence the use of the two kinds of insulin is preferred by the patient besides ensuring a more steady blood-sugar level throughout the day and night.

My thanks are due to Dr. Mary Leslie-Smith, pathologist to the hospital, who performed the blood-sugar estimations, and to Dr. Ruth Pike, house-physician, who organised the hospital experiments and took the blood for the estimations; also to Sir Robert Hutchison for his interest and helpful suggestions.

MEDICAL SOCIETIES

ROYAL SOCIETY OF MEDICINE

SECTION OF THERAPEUTICS

AT a meeting of this section on May 14 with Sir WILLIAM WILLCOX, the president, in the chair, a discussion on modern methods in the

Treatment of Cerebrospinal Fever

was opened by Dr. H. STANLEY BANKS, who demonstrated on the screen the data on which his present practice was based.

In 1937–38, when the treatment was serum intravenously and sulphanilamide by mouth, there was a gross fatality-rate of 16·9 per cent. in 71 cases. In 1938–39, when either sulphanilamide or sulphapyridine was used without serum, the gross fatality-rate in 80 cases of similar age-grouping was only 6·25 per cent. On this and other clinical evidence he was unable to detect any practical advantage to be gained from serum administration provided that the drugs were used in correct dosage. In the present year he had treated 120 cases of all ages from infancy to over 70 years, and the gross fatality-rate was 10 per cent. These epidemic cases contained a much higher proportion of acute cases than the former series, and 93 per cent. were group I infections, compared with 65 per cent. before the epidemic. Petechial and purpuric rashes were present in no less than 46 per cent. and there were many with large hæmorrhages. The complications were not serious, apart from two cases of deafness, one absolute and one partial; those which cleared up included eleven cases of polyarthritis, two of glycosuria with ketosis, two of multiple vesicles and ulcers in the purpuric areas, one of severe myocarditis with gallop rhythm, several cranial-nerve palsies involving III, IV, VI and VII, and Jacksonian convulsions in six cases which recovered. The drug effects included three cases of hæmaturia, eight of drug rash and fever, and twenty-six of nausea and vomiting which cleared up when the drug was changed to sulphanilamide. One case of granulopenia was discovered on the day after the drug treatment stopped (ninth day) but 24 hours later the polymorph-count began to rise rapidly. Provisional figures supplied to him by the Ministry of Health, and subject to some amendment, for the first quarter of 1940, in England and Wales were: civilian cases 4388; deaths 1040; fatality-rate 23·7 per cent.; non-civilian cases 705; deaths 80; fatality-rate 11·3 per cent. The age-group fatality-rates of 787 cases treated with the drugs alone or in combination with serum which had been reported to the Ministry of Health showed the highest fatality-rates to be in infants (49·2 per cent.) and over the age of 45 years (50 per cent.). The fatality-rate for the whole series at all ages was 22 per cent.

Dr. Banks showed that the main cause of death in his series, accounting for six of the twelve deaths, was the encephalitic type of disease, characterised by rapid onset of coma, purpuric rash and a short course to a fatal issue generally in 15–36 hours. Post-mortem there was little or no meningeal exudate but the whole brain showed congestion, œdema, hæmorrhage, widespread capillary thrombosis and degeneration of nerve-cells. In two cases of the six there was also adrenal hæmorrhage, and in these the pulse had been imperceptible on admission to hospital. This might be called the "encephalitic-adrenal" type. It was known in the United States as the Waterhouse-Fredericksen syndrome. Dehydration in young children was another common cause of death but it could be prevented. His conclusions as to treatment were:

(1) Sulphapyridine by mouth is the drug of first choice. If, however, it causes vomiting twice, nausea, depression or hæmaturia, it should be immediately changed to sulphanilamide. This was necessary in about a quarter of the cases admitted and was almost invariably successful. It was better policy than that of substituting intramuscular injection of the sodium salt, since the latter caused necrosis of muscle-fibres and ulcers and sloughs of subcutaneous tissue. Since sulphanilamide is a less potent drug, dosage must be high for the first three days and gradually reduced.

(2) The period of administration need rarely exceed 6–7 days.

(3) Intravenous sodium solution of sulphapyridine in two initial doses of 2 g. for an adult, diluted in three volumes of saline, is recommended for very acute cases and where the drug cannot be given by mouth or nasal catheter.

(4) Spinal drainage for two or three days is desirable in a small proportion of cases to relieve pressure symptoms—e.g., slow pulse and respirations, headache and restlessness.

(5) Fluid administration, especially to small children, is of major importance in order to prevent or relieve dehydration. The technique of the nasal and pharyngeal tube should be mastered. In dehydration delay in giving parenteral fluid may be fatal. The intraperitoneal route is often convenient and should be more widely used. Repeated vomiting as a cause of dehydration can be prevented by change of drug.

(6) Acute coma, accompanied by a purpuric rash —symptoms suggestive of the encephalitic type— should be an indication for immediate sulphapyridine treatment pending admission to hospital.

Dr. G. EMRYS HARRIES described the treatment of 200 cases this year in Cardiff. Their ages ranged from 10 weeks to 70 years. There were 22 deaths, giving a case-fatality rate of 11 per cent. The cases were generally more severe than sporadic cases in former years. Petechial hæmorrhages were present in 41 per cent. Group I strains were isolated in 90 out of 93 cases. Complications included bronchopneumonia, iridocyclitis, bilateral nerve deafness, orchitis, adrenal hæmorrhage, arthritis, transient hemiplegia and other transient paresis. Treatment consisted of 2 g. sulphapyridine by mouth on admission, repeated after four hours, and then 1 g. four-hourly for 72 hours; then, if the sugar content of the C.S.F. was approaching normality, 0·5 g. six-hourly for 24 hours followed by 0·5 g. t.d.s. for three or four days. Children under 12 had half the adult dose. To comatose patients the crushed tablets were given in nasal feeds. For vomiting, the sodium solution was given by intramuscular injection. In severe cases the sodium salt was given intravenously in 0·5 to 1 litre of 5 per cent. glucose saline by the drip method. No serum was given intrathecally, but 30–60 c.cm. meningococcal antitoxin was given intravenously in severe cases. Fluids were pushed, as dehydration might be fatal. Cases in coma up to 10 days were given fluids by nasal feeds at four-hourly intervals, and recovered. In fulminating hæmorrhagic cases cortical extract and large amounts of saline were given intravenously in order to support sodium metabolism. Three patients whose pulse was imperceptible on admission recovered under treatment on these lines. As a sedative sodium bromide was given instead of potassium bromide. No masks were worn by attendants owing to the risk of induction of nasopharyngeal congestion and lowered resistance. He uttered a word of warning against small doses of sulphapyridine as a prophylactic in suspected cases.

Dr. W. R. THROWER pointed out that the sodium solution of sulphapyridine had an alkalinity equivalent to N/10 caustic soda. He showed sections to illustrate necrosis of muscle-fibres after intramuscular injection, and epithelialisation of a sinus after subcutaneous injection.

Lord HORDER referred to the encephalomeningitic type and the septicæmic type as two extremes between which occurred the bulk of the meningeal cases. He emphasised the need for drainage especially in cases treated at a late stage. Years ago he had demonstrated to colleagues the simplicity and advantages of intraperitoneal injection and he supported the suggestion that this route should be used for fluid administration.

Dr. MERVYN GORDON, F.R.S., recalled that the epidemic of 1915 had been due entirely to the type I meningococcus. Type II was quite a different organism which absorption tests showed to have an affinity with the gonococcus. From so-called sterile cerebrospinal fluids he had sometimes found the meningococcus to grow after four days in glucose broth. He remarked on the difference in the case-fatality rates obtained by experts and those shown in the Ministry of Health's figures for all cases. Just as in the days of serum treatment, so now the best results in this disease were obtained by expert treatment. He considered that there should be a definite plan for diffusing this new information and applying it.

Flight-Lieutenant WILLIAMS stated that of his 45 cases of the favourable age-group represented by airmen, he had not had a single death. He used high dosage of sulphapyridine for three days and gradually reduced it. In a controlled experiment he had found no advantage in repeating lumbar puncture after the first diagnostic one. He considered clinical signs of response to treatment more reliable than sugar estimations of the C.S.F.

Dr. GERALD SLOT asked whether isolation was necessary. Could this disease be nursed in a general hospital?

Dr. J. A. STRUTHERS called attention to possible fallacies in the published figures for weekly notifications and deaths in London.

The PRESIDENT considered that drainage by lumbar puncture had still its value. He observed that even purulent arthritis cases generally cleared up. He used Prontosil soluble as an intravenous injection but had doubts as to the potency of Soluseptasine.

Dr. BANKS in reply stated that case-to-case infectivity was low. In his opinion, the most important point in management was not isolation but treatment in skilled and experienced hands. Treatment should be centred wherever this could be found. He considered that sodium solution of sulphapyridine was the most potent agent for intravenous injection.

Dr. HARRIES in a brief reply mentioned that of his 200 cases this year lumbar puncture had been accomplished in all without a general anæsthetic.

REVIEWS OF BOOKS

Sclerosing Therapy

Injection Treatment of Hernia, Hydrocele, Varicose Veins and Hæmorrhoids. Edited by FRANK C. YEOMANS, M.D., F.A.C.S., professor of proctology and attending surgeon, New York Polyclinic medical school. London: Baillière, Tindall and Cox. 1939. Pp. 337. 27*s*.

IN this book a mass of information is gathered together about the four surgical conditions that have proved amenable to cure by injection. The editor is the author of the section on hæmorrhoids, and he tells the novice clearly and concisely when, where and how to inject. Unfortunately he has not kept a restraining hand on his co-authors. In the section on hernia it is difficult to acquaint oneself quickly and accurately with the precise steps of the technique. The instructions for carrying out the actual injection are placed as foot-notes to the illustrations—a clumsy method of imparting information, especially as there is no summary in the text. It would be possible to read the chapter on technique without realising the importance of making sure that the hernia is completely controlled by a truss throughout, and without being certain which end of the inguinal canal to start injecting. The anatomical relations of the hernial sac should have been more precisely described, for in injection treatment they are all-important. The differential diagnosis of inguinal and femoral hernia, which can be a pitfall for the uninitiated, is worthy of more than the cursory mention given it. And it hardly seems wise to teach that a strangulated hernia is "one which may or may not be reducible." For the sake of the inexpert practitioner these defects should be corrected in an account that has evidently been prepared with much care, and is well illustrated.

The author of the section on hydrocele is probably right in saying that sclerosing therapy in this condition may replace operation, for it is far more straightforward than the injection of hernia. The few difficulties are clearly set out here. The hundred pages on varicose veins are a mine of information, and every complication before and after injection is dealt with.

There is no doubt a place for a book on sclerosing therapy, but a simple account of technique and complications would perhaps have made a wider appeal than a work as elaborate as this.

Textbook of Occupational Diseases of the Skin

By LOUIS SCHWARTZ, M.D., medical director, United States Public Health Service, in charge of dermatoses investigations, and lecturer, department of dermatology and syphilology, New York University, college of medicine; and LOUIS TULIPAN, M.D., clinical professor of dermatology and syphilology in the college. London: Henry Kimpton. 1939. Pp. 799.

TEXTBOOKS on occupational diseases of the skin are mostly nothing more than grim catalogues only meant for reference, but Dr. Schwartz and Professor Tulipan have produced one which makes fascinating reading. They have proved that to elucidate the problems of the occupational dermatoses some knowledge of the industrial processes involved is necessary and with this end in view they have visited hundreds of factories and workshops. Their accounts of these processes are simply written and easily understandable. In this branch of dermatology the instincts of a detective are also required and there are numerous examples of the authors' skill in this direction. They attach great importance to patch testing, and it is a pity that this simple procedure is not more often employed at an early stage in cases of industrial skin disease in this country. In cases of mild occupational dermatitis arising early in employment the authors recommend that the workmen should continue with their work and so acquire an immunity to the irritating substance. This recommendation should be accepted with reserve, for the usual experience is that such a course leads to aggravation of the skin eruption.

The book contains full and useful bibligraphies and is undoubtedly an important contribution to dermatological literature.

Sexual Perversions and Abnormalities

By CLIFFORD ALLEN, M.D. Lond., M.R.C.P., D.P.M., assistant physician to the Tavistock Clinic. London: Humphrey Milford, Oxford University Press. 1940. Pp. 193. 7*s.* 6*d.*

WRITING on the subject of this book was at one time evidence more of personal courage than of scientific endeavour. Since then the prejudices have been largely removed and modern genetics, endocrinology and psychological observations in higher animals and children should now be able to provide a scientific basis for a psychiatric outline of the anomalies of sex in man. Dr. Allen here tries to lay down such a basis, but the result is not wholly satisfactory. He deliberately omits endocrinology from consideration because "the laboratory worker finds the problem artificially simplified." With genetics he deals incidentally on two pages, and he makes small use of the wealth of material in infant and child psychology collected in the last twenty years. There is an instructive chapter on sexual development in the subhuman primate, reviewing the observations of Zuckermann, Koehler and others.

By far the largest space is given to Freud's theories of sexual development and to the psycho-analytical interpretations of the perversions. The book contains many quotations from Freud and still more from minor psycho-analytic writers, which make no easy reading. Some of these "cuttings" appear to have been collected in a hurry. For instance, more than a page is filled with a psycho-analytical classification of types and causes of frigidity, and at the end the author remarks that it is of little value. Here and there one finds criticisms of Freudian views, often rather lukewarm; but the interpretation of ten "representative cases" reported is predominantly psycho-analytical. All but two have been successfully treated by the author. Dr. Allen says he specialises in the treatment of prepsychoties, yet he seems uninterested in the important relations of sexual perversions to the major psychoses and to drug addiction, though just in these fields a certain amount of reliable clinical observation has been accumulated.

Some of Dr. Allen's psychiatric statements challenge opposition—for example, that alcoholism in manics is the result of their increased sexuality. He invites misunderstanding when he speaks of the taboo against sex present "in excessively narrow religious families" as ending in paranoid schizophrenia. And his belief that psychotherapy of a sexually abnormal patient can prevent him from falling into a grave psychosis will not be shared by many experienced psychiatrists. The concluding chapter on prevention and treatment makes up for some of the disappointment caused by the book's scientific window-dressing in offering plain, sound and practical advice, besides recommending deep transference analysis as the "sheet anchor" of treatment in sexual abnormalities.

Mineral Metabolism

By ALFRED T. SHOHL, M.D., research associate in pediatrics, Harvard University. London: Chapman and Hall. 1939. Pp. 384. 30*s.*

SINCE Voit and Rubner laid the foundations of the subject there have not been many books on mineral metabolism and no comprehensive reviews have appeared for ten years or more. Time was ripe, therefore, for another, for there have been great discoveries in the last decade. Dr. Shohl's book is characteristically American in style, outlook and arrangement. There is an introduction, in which the author wisely includes a section on terms and definitions, and this is followed by chapters on the mineral composition of the body, secretions and excretions, internal secretions, total base, chloride, ammonium and bicarbonate, calcium and magnesium, phosphorus, sulphur, iron, iodine, traces, water metabolism, anion-cation relationships, and mineral intakes, balances and requirements. Each chapter ends with a bibliography. There are some blemishes in this painstaking piece of compilation. Too many of the references are to American authors. Only a passing reference is made to sodium-chloride deficiency in man and there is no mention of the experimental reproduction of the syndrome. In the chapter on the trace elements there is no description of the effect of copper in curing sway-back disease in lambs or the possible implications of this discovery on the whole problem of demyelination. There is no reference to the discovery that cobalt cures coast disease in sheep, although this is a proven fact of great economic importance. Nothing is said of the presence of barium in the eye tissues of oxen, and the account of zinc is far from up to date. Nevertheless, there is a great deal to praise in the book and it can be certain of a welcome from both teachers and research workers.

THE LANCET

LONDON: SATURDAY, MAY 25, 1940

SUPPLY AND DEMAND

THE Army needs more doctors, and though no doubt they will soon get them, it is regrettable that they must appeal in this way as if doctors were mere comforts, like woolly mittens. The medical profession is a most patriotic body, and it may surprise the layman that its members need any persuasion at this stage to don uniform. When war broke out doctors did, in fact, respond magnificently, but their ardour was damped by disappointments, some due to the unexpected mildness of the enemy's attack and therefore unavoidable. Those who joined the Army sometimes found themselves marking time and the news spread to potential volunteers who felt they were doing more useful work where they were. But now that active warfare has come there should be no danger that the doctor who volunteers for service will find his efforts wasted—there is every prospect that they will be extended to the utmost. The need is now a real one and the object must be to see that the places are filled by the doctors most fitted to fill them. It is questionable whether the present system whereby doctors are on the same footing as fighting men will attain this object. A doctor is not qualified until several years after the age at which he could have been a first-class fighting man. Under the age of 30 he is unlikely to have reached his full capacity as a doctor; he is often at his best when over 60. Although youth is necessary for the highest physical endurance, long periods of steady application to routine are often easier in middle age. For Army work a doctor of 37 would probably correspond in efficiency to a fighting soldier of 21. Even the necessity for physical fitness does not apply with the same force. There are doctors doing useful work in hospitals and elsewhere with disabilities which would disqualify them for the Army. And many jobs at the base could be done as well by women as by men.

There are good grounds then for placing doctors on a special footing as regards recruitment. A case might be made out for extending conscription to doctors up to 55, so that the local medical war committees could make up their quotas from the majority of the doctors in their areas, and not be confined to young men and older volunteers. But whether actual conscription is necessary or not is a minor point. Many no doubt object strongly to compulsion, though others would be glad to be relieved of the necessity to decide between the claims of their practices and families and their country. If the whole profession knew that it was efficiently organised a request from the central body to take up a particular duty would rarely be refused. With thorough organisation it should be possible to supply the armed forces and the E.M.S. with as many doctors of each type as they need and at the same time to ensure that doctors were not wasting their time in evacuated towns while others were working overtime in the reception areas.

The present distinctions between the different medical services should be abolished. We are involved in total war, and for efficiency unity and simplicity of organisation are essential. As Medicus, M.P., suggests after his tour of the B.E.F., doctors should all be enrolled in a unified and if necessary uniformed national service whose members could be drafted into whatever branch, civil or military, most needed them. The individual branches already exist. Their administrations are all there except for ordinary civilian practice. What is missing is the unifying authority, and even for this the organising machinery exists in the Central Medical War Committee and its complex derivative bodies. It should not be difficult to evolve a supreme committee from these. There is a widespread objection to state medicine, but state medicine under a bureaucracy in peacetime and a national service in war are very different things, and the danger of the thin edge of the wedge could be avoided by putting the service not under a government department but under a public utility board, with members nominated by the Services, the medical organisations, and through Parliament by the general public. Now is the time, before direct assault is made on us, to face the difficulties and inevitable confusion of the transition period, and Mr. MACDONALD might well make this his first concern in his new office.

THE POTENCY OF VITAMINS D_2 AND D_3

AT the last meeting in 1934 of the International Biological Standardisation Conference, organised by the Health Section of the League of Nations, trouble arose over the vitamin-D standard because vitamin D from irradiated ergosterol and vitamin D in cod-liver oil did not have the same relative potency in rats as in chickens, while it was not known for certain what their relative potency was in human beings. In the end the conference arranged provisionally that, while a solution of irradiated ergosterol should continue as the international standard, a sample of cod-liver oil should be available as a subsidiary standard, and it recommended that the anomalous action of vitamin D from different sources should be further investigated.[1] Since 1934 a great deal has been learned, and but for the war the problem would have been discussed again six months ago. Much of the investigation has been done here and abroad in the normal course of research, but some special inquiries have been instituted by the accessory food factors committee appointed by the Lister Institute and Medical Research Council. The National Institute for Medical Research at Hampstead stands in a special relation to the International Biological

1. *Quart. Bull. Hlth Org. L.o.N.* 1934, 3, extract 15.

Standardisation Conferences, and the work of preparing for and organising the conferences falls largely upon British workers. Two papers that we publish this week answer at least in part the question whether vitamin D from different sources has the same relative potency in human beings as in rats. The question has been in doubt ever since irradiated ergosterol and cod-liver oil have both been available for the treatment of human rickets. Since 1934 the outstanding event in this field has been the identification by WINDAUS and his co-workers [2 3] of irradiated 7-dehydrocholesterol with the vitamin D (D_3) commonly found in fish-liver oils. The vitamin was isolated from natural sources and synthesised from cholesterol, and a supply of it was made available before the war to Sir HENRY DALE for research in this country. Obviously this pure material, for which maximum potency for both rats and chickens was claimed,[4] would have many advantages if adopted as the international standard instead of vitamin D from irradiated ergosterol, now called vitamin D_2.

When changes such as this are contemplated in any of the international standard materials it is essential to know as accurately as possible the biological potency of the new substance in terms of the old. The error of all such biological tests is high, and it is therefore usual to invite a number of different laboratories to make the comparison independently and, if necessary, to obtain a statistical assessment of the pooled results. The vitamin-B_1 standard was recently changed in this way from an acid clay adsorbate of the vitamin to pure synthetic vitamin B_1 hydrochloride after a collaborative biological test organised by Dr. T. F. MACRAE of the Lister Institute. For vitamin D_3 such a combined comparison with vitamin D_2 was similarly organised by Dr. K. H. COWARD of the Pharmaceutical Society. The results, which are shortly to be published,[5] were extremely satisfactory, since there was excellent agreement between the different laboratories, and the findings of WINDAUS and his colleagues were confirmed. The value for vitamin D_2 is by definition 40,000 I.U. per gramme, and the value for vitamin D_3 was found to be the same. The material thus tested was then available for testing the relative potency of these two forms of vitamin D in human beings. In 1937 it seemed fairly certain that for the human infant vitamin D from fish-liver oils, irradiated ergosterol, irradiated cholesterol, and vitamin-D milks of various kinds, had the same relative potency as for rats,[6] but this conclusion is not generally accepted as beyond question and there is a recurring tendency to attribute greater potency to vitamin D_3. The difference in potency is certainly not great, if it exists at all, but a superiority of 50 to 100 per cent. is difficult to establish with certainty because the large error of the most carefully planned animal studies is greatly increased when the experimental subjects are human beings. To obtain a satisfactory comparison the subjects must be as similar as possible, and the doses must be chosen so that the minimum curative dose of each substance is established. It is easy to show whether vitamin D_2 and vitamin D_3 will both cure osteomalacia and rickets, but it is not at all easy to determine the smallest dose of each which will cure at a certain speed.

Three different criteria were chosen in this investigation for measuring the curative efficacy of the two vitamins: cure of rickets in infants, cure of osteomalacia in adults in India, and the relief of tetany after parathyroidectomy. The first subject was inquired into by MORRIS and STEPHENSON,[7] who chose a dosage of 2000 I.U. daily, which they reckoned to be on the low side. With this dosage they treated two groups of six rachitic children, one with vitamin D_2 and the other with vitamin D_3. They reported no difference in the response of the two groups, but unfortunately they obtained no evidence whether 2000 I.U. daily really approached the minimum curative dose for either substance, or whether if a smaller dose had been given healing would have been equally slowed for both the vitamins or more for one than the other. Dr. WILSON has now treated fifteen pairs of cases suffering from osteomalacia or late rickets with large single weekly doses of 10,500 or 21,000 I.U. of vitamin D_2 or D_3. She made a valiant attempt to ascertain the minimum curative dose of each of the vitamins but was defeated by the refusal of the patients to continue treatment when the rate of cure was definitely slowed. When the large doses were given it was certain that no difference could be detected. In five pairs of cases, however, the small dosage of 10,500 I.U. once a week was persisted with for several weeks and of these, cure was thought to be more rapid with vitamin D_3 in three pairs, with vitamin D_2 in one pair, and in the fifth pair the rate for the two vitamins appeared to be the same. The numbers are too small to draw conclusions, but, as always, the difference if there is one is in favour of vitamin D_3. In the second study Professor HIMSWORTH and Dr. MAIZELS have treated a case of parathyroid tetany alternately with vitamin D_2 and vitamin D_3, trying to ascertain the minimum dose of each which would control the tetany. The patient was particularly suitable for the purpose because he had been under observation since the beginning of 1934. It had been ascertained by long trial that a weekly dose of 500,000 I.U. of vitamin D_2 was necessary to maintain his blood calcium at 8·4 mg. and his plasma phosphate at 3·2 mg. per 100 c.cm. It was thus not difficult to change the treatment and determine the minimum dose of vitamin D_3 which would have the same effect. With a weekly dose of 250,000 I.U. of vitamin D_3 the calcium fell to 6·8 and the phosphate rose to 4·7 mg. per 100 c.cm. When the dosage was

2. Windaus, A., Lettré, H. and Schenck, F. *Ann. Chem.* 1935, **520**, 98.
3. Brockmann, H. *Hoppe-Seyl. Z.* 1936, **241**, 104.
4. Schenck, F. *Naturwiss.* 1937, **25**, 159.
5. *Quart. Bull. Hlth Org. L.o.N.* in the press.
6. Hume, E. M. *Nutr. Abstr. Rev.* 1936–37, **6**, 891.
7. Morris, N. and Stephenson, M. N. *Lancet*, 1939, **2**, 876.

increased to 500,00 I.U. the calcium value rose again to 8·8 and that for phosphate fell to 3·2 mg. per 100 c.cm. In this most satisfactory experiment the possible difference in potency of the two vitamins, at any rate for this physiological purpose, is narrowed down so far that the probability of its non-existence is strong.

Even after these special studies it is still not possible to say with absolute certainty whether vitamins D_2 and D_3 have the same relative potency in human beings as in rats. NITSCHKE [8] has recently drawn attention to what appears to be a definite difference in the behaviour of the two vitamins. He tried to cure rickets in children with large single intramuscular injections of vitamin D_2 or D_3 and found that the former was almost inactive when given in this way. Of four other workers who made the same comparison three got the same result as he did, while only one (NADRAI) found vitamin D_2 effective when injected. NADRAI, however, used a Hungarian preparation which may have contained vitamin D_3 also, while the other four workers used Vigantol Merck. NITSCHKE concludes that in the process of absorption from the human gut, vitamin D_2 is subjected in the intestinal wall to some change which renders it active. Studies with monkeys might have yielded helpful evidence but these have been few. LUCAS, HUME and SMITH,[9] from clinical observations on the prophylaxis of rickets in pet monkeys, express doubt whether vitamin D_2 is very effective, and GERSTENBERGER and co-workers [10] claim that vitamin D_3 is decidedly superior for Rhesus macaques, though they give no clue as to the nature of their experiment. In spite of all this work the problem cannot be regarded as settled. Very likely it is impossible to settle it by existing methods because any difference that there is lies within the error of the biological technique.

FOOD POLICY

THE hands of the Ministry of Health have been so full since war began that they have had little time to advise on the nutritional needs of the people, and the question of how best to make supply fit demand has been left to the Ministers of Food, Agriculture and Shipping. If the scientific side of nutrition had been more to the fore on the kitchen front the fourth report of the Select Committee on National Expenditure [11] might have been less critical. The committee point out that the Ministry of Food has grown up piecemeal as the need for each part has become manifest. At the head of each commodity division is an expert in his own particular trade. The policy has been to provide the public with as wide a variety of foodstuffs as possible, and where there has been competition between two commodities the balance has been struck by a process of compromise rather than by a scientific decision as to which of the two is the more dietetically valuable. The controller of each commodity has been concerned largely with not letting his own trade down, and if the nutrition of the nation is at last to be put on an optimum war-time basis many trade interests will have to suffer severely. The committee give sugar as an example. They asked Ministry of Food officials whether sugar would not have a better chance of being distributed to the greatest advantage if it were mixed with cocoa to make chocolate or with fruit to make jam than if it were used in boiled sweets or for icing cakes. The committee were assured that the Ministry recognised this point and that chocolate-makers had therefore been allotted 70 per cent. of their normal requirements as compared with the boiled-sweet makers' 60 per cent. There was, says the report, a pull-devil, pull-baker business between the makers of condensed milk and boiled sweets and the pastry-cooks. The solution the committee proposed is an authoritative body of scientists and practical men to work out a basic plan of war-time food policy for the country. This would aim at providing an adequate diet at the least possible cost in shipping and foreign currency. It would then be for the Ministry of Agriculture to supply as much of the menu as possible from home production leaving the residue to be completed by the Ministry of Shipping. The final transfer from the warehouse to the larder on a basis that would be fair for all would be the concern of the Ministry of Food.

SULPHUR AND CHEMOTHERAPY

SULPHÆMOGLOBIN is less often found in the blood in significant quantities after the administration of sulphanilamide and its derivatives than methæmoglobin, but while methæmoglobin disappears within one or two days of stopping the drug sulphæmoglobin persists for from four to six weeks. During that time it immobilises part of the hæmoglobin, so that in its effect it is the equivalent of an anæmia. There is good reason, therefore, for avoiding sulphæmoglobinæmia, but there is some difference of opinion as to how this should be done. The condition is known to appear in patients receiving sulphanilamide who have much sulphuretted hydrogen or soluble sulphide in their alimentary tract. The presence of these has been thought to be due to an excess of combined sulphur in the diet, and various dietetic prohibitions have consequently been introduced. Some doctors forbid eggs, others eggs and onions, and others again prescribe a low residue diet in addition. The egg theory seems to be based on a misconception. It is true that the bacterial decomposition of eggs outside the alimentary tract gives rise to sulphuretted hydrogen, but in normal digestion the sulphur-containing amino-acids are absorbed with very little formation of sulphides. It has never been shown that eggs in the diet promote the formation of sulphæmoglobin when the intestine is normal. The same applies to other foods containing sulphur, many of which, such as cheese, contain more than eggs. Another prohibition, which is sound though not for the reason usually given, is that of Epsom and Glauber's salts. These

8. Nitschke, A. *Z. Kinderheilk.* 1939, **61**, 385.
9. Lucas, N. S., Hume, E. M. and Smith, H. H. *Proc. zoo. Soc. Lond.* Ser. A. 1937, part 2, 205.
10. Gerstenberger, H. J., Chapman, E. E., Kerbaugh, J. L. and Rose, C. S. *Sci. Proc. Amer. Soc. Pharm. exp. Therap.* March 13, 1940, p. 15.
11. Report of the Select Committee on National Expenditure H.M. Stationery Office. 1940. 1*s*.

lead to sulphæmoglobinæmia not because the sulphates are reduced to sulphides but because they are purgatives. When purgatives are given the fluid contents of the small intestine are hurried into the colon and it is the bacterial decomposition which takes place in these liquid fæces that produces the sulphides. Certain drugs, of which phenacetin is most used, predispose to the formation of methæmoglobin, and, if even small quantities of sulphides are present, of sulphæmoglobin. Confection of sulphur administered by itself rarely results in sulphæmoglobin appearing in the blood, but if the sulphur is given with sulphanilamide sulphæmoglobin soon appears, and it appears rapidly if phenacetin is given as well. Drugs like phenacetin must therefore not be used with sulphanilamide, but aspirin is harmless in this respect. To sum up, then, when giving sulphanilamide and the like purging and phenacetin should be avoided, but there is no reason why the patient should not have as normal a mixed diet as his condition will allow.

ANNOTATIONS

JUVENILE RHEUMATISM

WHILE necessity was the mother of evacuation, such a measure might well have been fathered in more peaceful times by those interested in the prevention of disease in general and of juvenile rheumatism in particular. The latter is notoriously a disease of the "hospital class," especially of those who live in overcrowded and low-lying districts, and prevention means slum clearance, or alternatively child clearance. The part played by overcrowding is brought out in both the comprehensive pre-war survey of London juvenile rheumatism[1] and the recent Dublin survey.[2] In Dublin the heaviest incidence of non-choreic cases is seen in the poorer and more densely populated areas less than 50 feet above Liffey-level. Since this is an evil not to be remedied under present social conditions, except apparently under the still greater evil of war, mitigation is our only resource. In 1936 three supervisory clinics and a small convalescent unit of twenty beds were set up to work in conjunction with hospitals and public-health authorities. The value of such a rheumatism scheme, as Bach and his associates point out, must be measured by its success in reducing the incidence of permanent cardiac damage. That worth-while results are possible is suggested by the gradual and progressive reduction of the incidence of such damage in London elementary-school children from 1·9 per cent. in 1927, when the L.C.C. scheme was started, to 0·77 per cent. in 1937. In London the first substantial reduction occurred four years after the inception of the scheme, so that the incidence of rheumatic heart disease in Dublin (0·5 per cent.) over the first three years of their scheme should show further reduction in the future, even though the total number of cases of juvenile rheumatism remains, as it did in pre-war London, about the same. In England and Wales, however, here and now, there has been since the outbreak of war a considerable reduction compared with last year in the incidence of scarlet fever. This is particularly obvious in the large cities, as Dr. Alison Glover[3] pointed out in his presidential address to the Royal Society of Medicine on April 5, and all the more striking by reason of a rise in the figures for Eire and Northern Ireland. We may hope, perhaps, that the hæmolytic streptococcal infection which invariably precedes an attack of rheumatic fever will likewise be less often seen, as another good result of evacuation.

NERVE SUTURE

MUCH attention was given to nerve suture in the last war, but the disturbing fact remains that the most meticulous technique still cannot ensure success. Leriche[4] has lately examined the possible causes of failure. Anatomical continuity is, as he says, of no avail unless return of function follows. He believes that ischæmia at the point of repair accounts for many failures. In order to ensure accurate apposition there is a tendency to strip the nerve ends from their bed for some distance above and below the lesion, and this may easily destroy their fine vascular connexions. It is also fatal to put too much trust in the power of the nerve to withstand stretching. A gap of 2 cm. will impose too much strain to allow of successful end-to-end suture, and Leriche would not attempt direct suture if the ends could only be brought together by traction. Grafting would be the ideal method to bridge the gap. The environment in which the damaged nerve lies has more to do with its chances of regeneration than is generally recognised. The best chance is for the nerve that lies snugly, free from scar tissue, in a vascular bed. This, in Leriche's opinion, explains the relatively frequent success of musculospiral repair better than the fact that it is less "mixed" than the ulnar and median nerves. Suture of the median nerve stands a better chance of success in the arm than in the forearm, where it lies among avascular tendons. For the same reason the ulnar nerve is badly placed for recovery at the elbow-joint. The displacement of a nerve to a position where it is buried in healthy muscle is therefore worth considering, and this is often done with the ulnar nerve, though in this case rather with the intention of relieving it from tension. The time required for a long stretch of nerve to regenerate is a factor against the recovery of its function. According to Harry Platt nerves sutured in the arm rarely reach functionally to the hand; while those sutured in the forearm have much more chance of reaching the fingers. Presumably by the time the dendrons reach the muscle-fibres at the extreme periphery these have undergone such irreparable change that no physiological connexion is possible. The damage to the fine innervation of joints may also be permanent, even when the nerves to the neighbouring muscles have recovered. Leriche quotes a case of Stopford's in which, though the median nerve had regenerated after suture, joint sensation was permanently lost, so that the patient could only move the fingers under direct visual control. Articular deformities developing in the denervated part may easily prevent full muscular recovery after nerve regeneration, and Leriche insists that orthopædic operations should not be left too late.

Despite the difficulties of nerve-grafting, this method will certainly be developed in the future. As Christophe and Laudron[5] point out, the problem is to find a graft easily permeable to nerve fibres. The preserved heterogenous graft, used in the method described by Nageotte, has not given good results: Leriche condemns it after trial. Better success has been obtained with the fresh graft obtained from an amputated human limb, though this method has its

1. Bach, F., Hill, N. G., Preston, T. W. and Thornton, C. E. *Ann. rheum. Dis.* 1939, **1**, 210.
2. Clarke, P. J. H. *Irish J. med. Sci.* March, 1940, p. 97.
3. See *Lancet*, April 13, 1940, p. 693.
4. Leriche, R. *Pr. méd.* April 3, 1940, p. 345.
5. *Ann. Soc. belge chir.* Séance June 25–26, 1939.

limitations. The difficulty is to find a graft of the right diameter, especially when a fresh graft from a dog is used. Gosset and Bertrand, quoted by Christophe, have reported success with grafts of rabbits' spinal cord. The graft is immediately fixed in formalin, washed in saline a few days before use, and then kept in alcohol till the time of the operation. However the graft is done, the aftercare of the denervated parts is of paramount importance if downgrowth of the nerve is to restore function.

ALKALIS IN PEPTIC ULCER VINDICATED

ALTHOUGH the use of alkalis in the treatment of gastric disorders dates back to long before the 17th century, treatment of peptic ulcer by neutralisation really began with the work of Cruvelhier in 1832. The beginning of the 20th century saw the use of alkalis widely established but the work of Sippy in the United States towards 1915 was probably responsible for the more thorough attempts that have since been made to secure continuous correction of acidity and the consequent improvement in medical treatment. The introduction of fractional gastric analysis has also facilitated the investigation of gastric cases as regards the acidity of the stomach contents after food and treatment, and the work of Rehfuss on the response of the normal stomach to varying foods was important in this respect. But it is somewhat surprising that the medical treatment of peptic ulcer has seldom been carried to its logical end. Few patients with peptic ulcer receive treatment by proper food and alkalis in such a manner that anything like complete neutralisation of the stomach contents throughout the twenty-four hours is secured. The very incomplete neutralisation effected by milk alone, or by milk combined with the popular alkalis has lately been demonstrated by Wyllie.[1] Observation of the actual acidity of the gastric contents at half-hourly intervals throughout the waking hours with various antacids established the outstanding value of magnesium trisilicate and aluminium hydroxide. A year ago Bennett and Gill[2] demonstrated the effective qualities of aluminium hydroxide gel, and their results are borne out by the observations of Wyllie. Whether magnesium trisilicate has advantages over aluminium hydroxide is not shown, but it seems to be established that these modern remedies are superior to many, if not all, of their rivals. It is important to note that Wyllie pays the same attention to food as he does to medicine. His work confirms that of others in demonstrating that six-ounce feeds of milk given every two hours with a drachm of aluminium hydroxide or magnesum trisilicate half an hour after each feed will produce complete control of free acidity in almost every case. With larger feeds and doses the intervals might be extended but even this is doubtful. This vindication of orthodox treatment is welcome from a school which had tended in recent years to revive the centuries old doubt as to its value.

VITAMIN B_1 FOR TIC DOULOUREUX

SINCE synthetic vitamin B_1 has been easily obtainable it has been used in the treatment of nearly every disease of the nervous system. Convincing results have been reported in certain forms of peripheral neuritis, but in other nervous diseases its value has been doubtful. There seems little doubt, however, that some patients suffering from spasmodic trigeminal neuralgia gain relief from the vitamin, and the experience of Borsook, Kremers and Wiggins[3] suggests that the results are best if large doses are given by injection for a long time. They advise giving 10 mg. of vitamin B_1 (thiamin chloride) daily by the intravenous or intramuscular route, and an injection of liver extract three times a week, making up a weekly total of 22·5 U.S.P. units. They prescribed a high vitamin and low carbohydrate diet with 30 c.cm. of an aqueous concentrate of rice polishings daily by the mouth, providing 1500 international units of vitamin B_1 as well as other components of the vitamin B complex. They report 58 cases which have been under observation and treatment for from six to fourteen months, and 37 of these were "markedly improved." But the authors say that the treatment may have to be continued for as long as six months before the maximum benefit is obtained. The pain of tic douloureux shows so many spontaneous remissions that it is difficult to assess the value of a new form of treatment, especially when it has to be continued for several months. This regime is both expensive and laborious, but it has so far been justified by results.

MAKING BABY BREATHE

A BABY may fail to breathe when it is born either because its respiratory centre is depressed or because the stimuli needed for respiration have been applied too soon or are insufficient. Depression of the respiratory centre is most likely to be due to sedative drugs given to the mother. Premature respiration will be encouraged by anything that raises the fœtal carbon-dioxide concentration or by appropriate sensory stimuli. If the anæsthetic given to the mother is too light she may have a laryngeal spasm or may vomit, so raising her carbon-dioxide concentration to a level which will call forth an inspiratory effort from the baby. Exposure of the baby's body in breech deliveries or cæsarean section may also give rise to premature respiratory movements. In such cases the baby will breathe in liquor which may induce laryngeal spasm and may so coat the alveoli that the respiratory surface is seriously interfered with. An insufficient stimulus will produce asphyxia if the mother hyperventilates, as she is likely to do when anæsthesia is too light, so that her carbon-dioxide concentration is low. It then takes an unduly long time for the carbon-dioxide in the baby to reach the threshold level for stimulation of the respiratory centre. By then oxygen lack may have desensitised the centre, widening still further the gap between stimulus and threshold. Nosworthy[4] says it is unwise to promise any patient a painless labour, since in order to keep one's word one may have to give enough sedative to depress the baby's respiratory centre. A middle course between too light and too deep anæsthesia must be steered. The essential measures once the baby is born are to keep the infant head downwards, and to suck out liquor and mucus thoroughly from the upper air-passages. A stimulant to the respiratory centre, such as lobeline gr. 1/20, may be a great help and is used by some as a routine, although prompt and efficient drainage should be sufficient in most cases. Carbon-dioxide administration can be dangerous, for it is accumulating naturally and a further dose may raise the concentration to toxic levels. This gas also tends to quicken rather than deepen breathing. An ample supply of oxygen, on the other hand, is essential both to maintain life and to prevent the threshold of the respiratory centre rising too high. It should be given

1. Wyllie, D. *Edinb. med. J.* May, 1940, 336.
2. Bennett, T. I. and Gill, A. M. *Lancet*, 1939, **1**, 500.
3. Borsook, H., Kremers, M. Y. and Wiggins, C. G. *J. Amer. med. Ass.* April 13, 1940, p. 1421.
4. Nosworthy, M. D., *St. Thomas's Hosp. Rep.* 1939, **4**, 164.

under pressure to inflate the alveoli, either by squeezing a breathing bag attached to a face-piece, or by intubation. The latter method is far more efficient, and is easily applied once the simple technique is mastered. The direct vision method of Blaikley and Gibberd [5] may be used, or a blind oral method advocated by Nosworthy, which requires less apparatus and in his opinion is unlikely to do any damage even in unskilled hands. The left forefinger is introduced into the baby's mouth until the tip rests on the arytenoid cartilages. A No. 12 or 14 French open-ended gum-elastic catheter is then passed into the mouth with the free hand, its tip being deflected forwards into the glottis by the left forefinger, and through this the operator can suck mucus out of the trachea. The catheter is then withdrawn, the mucus blown out, and after a second intubation the lungs are inflated by connecting a bag to the catheter. Normal inflation of the lungs is brought about in the first few hours after birth by crying. In weakly infants who do not cry normally a vicious circle of oxygen want and carbon-dioxide retention may be set up, and Nosworthy feels that early intubation and pulmonary inflation may then save life.

IMMUNISATION AGAINST RICKETTSIAL DISEASES

WITH the possible exception of heart water, which according to Neitz [6] can be successfully treated in sheep by injections of Uleron, rickettsial infections resemble the virus diseases, other than lymphogranuloma inguinale and probably trachoma, in being entirely unaffected by chemotherapeutic drugs. It is therefore not surprising that much thought has been directed to the discovery of methods of immunising against rickettsial infections, more especially against exanthematic typhus in the Old World and Rocky Mountain spotted fever in the New. In opening a discussion on immunisation against rickettsias at the Royal Society of Tropical Medicine on May 16, Dr. F. Murgatroyd pointed out that two methods were now in use involving the injection of rickettsiæ either living, perhaps attenuated, or killed. For immunisation against exanthematic typhus living murine typhus rickettsiæ have been extensively used in North Africa, either coated with egg yolk and mixed with sodium phosphate as in Tunis (Laigret and Durand [7]), or treated with bile immediately before injection as in Morocco (Blanc and Baltazard [8]). As their source of rickettsiæ the latter workers first used fresh guineapig tissues, but more recently they have found that murine typhus rickettsiæ remain active for a considerable time when present in the dried fæces of rat fleas. The flea fæces are treated with bile immediately before injection. Dr. G. M. Findlay, who had recently visited Tunis, said that some three million natives in Morocco and Tunis have been treated with living murine typhus rickettsiæ by one or other of these procedures. Few reactions, it is claimed, have been recorded in natives, but when living murine typhus rickettsiæ are injected into Europeans about 30 per cent. of them show febrile reactions, some of them severe. In addition, Blanc's vaccine, when employed in Chile, gave somewhat unsatisfactory results, for of 800 people vaccinated 23 per cent. developed grave typhus and 5 died. While people who have suffered from murine typhus are solidly immune to exanthematic typhus, almost certainly for life, the exact value of living murine typhus rickettsiæ in bringing epidemics of exanthematic typhus to an end is still uncertain, since critical experiments with adequate controls have not yet been carried out. In the present circumstances living murine typhus rickettsiæ can hardly be used for immunising Europeans. Unfortunately killed murine typhus rickettsiæ produce little immunity in man against living exanthematic typhus rickettsiæ, but dead exanthematic typhus rickettsiæ, if injected in sufficient quantities, do produce immune bodies against living exanthematic rickettsiæ. The problem, therefore, has been to obtain enormous numbers of exanthematic typhus rickettsiæ. The first successful effort was made by Weigl [9] who injected lice with suspensions of *Rickettsia prowazeki* per rectum. After five or six days the intestines of the lice, then teeming with rickettsiæ, were removed, ground up, and treated with 0·5 per cent. phenol. Since nearly two hundred lice are required for the immunisation of a single human being, this method cannot well be applied on a large scale. Within the last year, however, certain other techniques have been developed in order to obtain sufficient numbers of rickettsiæ. Zinsser, FitzPatrick and Wei,[10] for instance, grew the organisms on agar slopes covered with a layer of mouse or chick embryonic tissue. Monkeys and guineapigs were successfully immunised with the rickettsiæ thus obtained after treatment with 0·2 per cent. formol in saline, and more recently Zia, Pang and Liu [11] in China have utilised such vaccines for human immunisation. A further development which is capable of exploitation on a large scale has been made by Durand and Giroud.[12] When exanthematic typhus rickettsiæa are injected intranasally into half-grown mice they set up an intense pneumonia, which after a few intranasal passages proves fatal within forty-eight hours. To obtain the greatest number of rickettsiæ the mice should be killed when their temperature falls to 30°–32° C. By differential centrifugation an almost pure suspension of rickettsiæ may be obtained which after treating with 0·2 per cent. formalin can be used as a vaccine. A number of people have now been immunised by this method both in France and in this country. Immunity is shown by the development of a positive Weil-Felix reaction, and by the presence of specific immune bodies against rickettsia. It is too early to say how long this immunity lasts, but it certainly seems to last longer than six months. If other rickettsial infections should appear in Western Europe it is possible that satisfactory vaccines could be produced by one or other of these methods.

5. Blaikley, J. B. and Gibberd, G. F. *Lancet*, 1935, **1**, 736.
6. Neitz, W. O. *Berl. Münch. tierärztl. Wschr.* 1939, **55**, 134.
7. Laigret, J. and Durand, R. *Bull. Soc. Path. exot.* 1939, **32**, 735.
8. Blanc, G. and Baltazard, M. *Rev. Hyg.* 1940, **61**, 593.
9. Weigl, R. *Arch. Inst. Pasteur Tunis*, 1933, **22**, 315.
10. Zinsser, H., FitzPatrick, F. and Wei, H. *J. exp. Med.* 1939, **69**, 179.
11. Zia, H. S., Pang, H. K. and Liu, P. Y. *Amer. J. publ. Hlth* 1940, **30**, 77.
12. Durand, P. and Giroud, P. *C.R. Acad. Sci. Paris*, 1940, **210**, 125.

BLOOD-TRANSFUSION IN NEW ZEALAND.—In 1937 a National Blood Transfusion Council was set up in New Zealand to organise a blood-transfusion service on a voluntary basis throughout the dominion. Since its formation 13 new branches have been established and over a thousand donors have been enrolled. In February the council issued its first bulletin which contains an account of a system of storage of blood which has been successfully undertaken by the North Canterbury branch. The hon. secretary of the association may be addressed at P.O. Box 25, Te Aro, Wellington, C.2.

PREVENTION AND TREATMENT OF WOUND INFECTION

VI

SURGERY OF INFECTED WOUNDS

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(*Continued from p. 937*)

TREATMENT OF WOUNDS UNSUITABLE FOR SUTURE

In a number of accidental wounds, and in the majority of war wounds, immediate closure cannot safely be attempted even after a débridement as thorough as the circumstances will allow. Operation may have been too late, it may have been incomplete, or the general condition of the patient may have been unsatisfactory. The alternative methods then to be considered are packing and immobilisation with the possibility of secondary suture if the progress is satisfactory, and partial closure over Carrel tubes.

The open treatment relies on the experience that a wound which has been carefully excised, but may still contain some organisms and devitalised tissue, can be relied on to escape any serious infection, and may often be brought into a safe condition for secondary closure if it is immobilised and left widely open. The treatment is essentially the same as that for a frankly infected wound except that in more recent cases a germicide is usually included in the dressing in the hope that infection may be averted or overcome. After débridement and careful hæmostasis the wound is packed evenly and firmly with strips of gauze, particularly in all pockets, recesses, and opened planes. The gauze may be soaked in 1/1000 proflavine solution, which is harmless to the tissues, or sulphanilamide powder may be spread over the wound surface before the gauze is packed in, from 5 to 15 grammes being used according to the size of the wound. Both these substances are powerful antiseptics, particularly against streptococci, and sulphanilamide has the additional advantage that it is absorbed and acts through the blood-stream up to 60 hours afterwards. Over the gauze pack an abundant dressing is applied, and the limb is then bandaged over the whole segment to apply firm pressure, and immobilised in a splint or plaster case.

At each visit to the wound the surgeon considers the patient's condition, his chart, the appearance and smell of the outer dressings, and the circulation of the limb beyond them. If all signs indicate that there is no infection, the patient is anæsthetised again after 48 to 72 hours and the packing gently removed. In a case suitable for closure the exposed tissues have a pale and slightly pickled appearance, but there is no sign of pus anywhere. The wound may then be closed, provided that the patient can be kept for at least another week, and that the stress of work allows him to be under constant observation. Deep catgut sutures should be avoided as far as possible and their place taken by mattress or X sutures of silkworm gut approximating the muscles as well as the skin. If the wound is at all deep one or more rubber strips should be laid in its main recesses and brought out between the stitches; they should be removed as soon as the appearance of the wound and the pulse-chart justifies it. If sterility is in doubt the wound should be treated as infected.

INFECTED WOUNDS

A different problem is presented by a wound that is infected either because it is seen too late for decontamination or because decontamination has failed. In such a wound the bacteria have already gained entry to the tissues, and the local and general mechanisms of inflammation have already been put in train. We can still get such a wound to heal, but it must be healing by second intention, and our aim is the simple one of hindering the bacteria and aiding the tissues in the task they have already undertaken.

We can kill bacteria by antiseptics, but it is unlikely that we can damage those in the living wall of the wound by any means that will not hurt the defence mechanism to an equal extent. We can successfully attack those that are free in the cavity and discharges from the wound, thereby depleting reserves and preventing the formation and absorption of toxins; but chemical destruction of these free bacteria has no manifest advantage over mechanical removal of them and the proteins on which they thrive, that is, over free drainage. This same free drainage will also aid the defence mechanism, by evacuating dead leucocytes and spent lymph, and allowing fresh supplies of both to arrive. At the same time, by resting the injured part, the reacting tissues are given their best chance to institute defence and repair damage.

The simple physiological principles of rest and free drainage are thus the basis of the treatment of infected wounds. Operation is necessary in all but the most superficial, but its scope is limited to the removal of dirt and obviously dead tissues, and to exposure of the deeper parts of the track. In the group are all degrees of infection from wounds that are only just too late for excision and suture to those that are suppurating or even gangrenous. The first may be treated by classical débridement, but are left open afterwards. Suppurating wounds must also be cleaned up, but transgression of the early defence zone must be avoided, and the knife therefore plays a small part. The track of the projectile must be laid widely open, as far as possible by separating fascial planes rather than cutting fresh structures. Fragments of projectile and clothing, dirt, blood-clot, loose bits of bone and unhealthy muscle are cleaned out, using the fingers and gauze swabs as far as possible, with occasional help from scissors, but there should be no attempt at cutting back to healthy bleeding tissues. The wound is converted as near to a simple cavity lined with viable tissues as its circumstances will allow.

Drainage may be by rubber tubes, gauze packing, or a combination of the two. Rubber tubes drain their track only, and may erode structures with which they are in contact. They are therefore of little use as the sole method of draining an infected war wound, and have their chief sphere in giving egress through gauze packing, to the discharge from some deep structure such as a damaged kidney or joint. Safe and effective drainage of an excised wound can be assured more simply by packing it widely open with gauze. The essentials are that the wound shall have been rendered of simple shape and as free of foreign matter and dead tissue as possible, that the gauze be packed into every recess and cleft, leaving no pocket in which discharges can accumulate and decompose, and that the wound be left undisturbed for several days or even weeks. Undisturbed packing means that the immobilisation of the part is not interfered with and that the wound surface is not traumatised by changed dressings, but it is possible only while there is no pus dammed behind it.

In comparison to the preparation of the wound beforehand, and the care with which the pack is inserted, its exact nature is relatively unimportant. Plain gauze, flavine gauze, gauze soaked in saturated sodium sulphate or hypertonic saline or mixed with crushed salt tablets, and gauze impregnated with Vaseline have all been recommended. Plain dry gauze is said to act as a capillary drain, but it will cease to do so after a few hours. Flavine gauze can destroy a number of bacteria in the tissues with which it is in contact, and forms an excellent packing in the type of wound so lightly infected that delayed primary suture is hoped for; in heavier infections it ceases to be an antiseptic, and, like plain gauze, becomes soaked with discharge. Hypertonic packs, while making no claim to antiseptic action, are able to promote an outward flow of tissue fluids and where crushed salt is used this flow is evident for a week;

salt packing has therefore special advantages as the first dressing in a wound already heavily infected. All three dressings are eventually saturated with pus and become bacterial hives. Vaseline gauze has no capillary, antiseptic, or osmotic action, but it adapts itself to any shape, keeps the wound surfaces apart, and allows the discharges to escape past it to the outer dressings; it does not stick to granulations but is slowly extruded as the wound heals. The surgeon who has once made vaseline his friend comes to admire its almost human power to do what is wanted, and its more than human willingness to get out when its job is over.

Once an infected wound has been cleansed, laid open and packed it should be disturbed as little as possible, and should be exposed only if there is doubt as to its progress or when the dressings become offensive. An abundant covering of sterile gauze and wool is therefore put over the packing and the whole part is immobilised. The exact mechanism of immobilisation is less important than its efficacy. In the last war the French used plaster-of-paris extensively, while the British relied on splints, chiefly the Thomas. Now that we are familiar with the experiences of the Spanish war and have used plaster-of-paris in the treatment of osteomyelitis for some time it is likely that we will use it also to immobilise war wounds. The advantages of the method are many. The use of plaster for immobilising all wounds greatly simplifies the question of medical supplies. A plaster case gives absolute and unchangeable immobility, allows the patient to be sent in comfort and safety for any distance, and discourages meddlesome interference with his dressings by those who handle him in transit. The disadvantages must, however, not be glossed over. The dreadful smell of an undressed wound, which is not peculiar to this method but is the outward and odorous sign of physiological wound treatment, is worse and appears earlier with a plaster case because the discharges do not dry but are cultivated at body heat. A fracture accompanying a wound is immobilised by plaster but not controlled as adequately as by an extension splint, and shortening or other deformity is likely. Where there is no fracture a plaster case does not immobilise a limb any better than well-applied Cramer's splinting, and it takes much longer to apply. The value and application of traction splints of the Thomas type, and of pliable gutter splints such as Cramer's wire ladders, is well known, and it will be surprising if they do not hold their own in this war. Doubt arises about the Thomas arm splint, so called, for it was a war device, and did not arise in Liverpool but acquired a spurious orthodoxy from its assumed name; this splint, in the opinion of many, holds the arm in an uncomfortable and un-functional position, cannot extend efficiently without at the same time compressing the axilla, is much in the way during transport, and immobilises the upper limb less completely than bandaging to the chest.

THE CARREL METHOD

The method of intermittent irrigation devised by Carrel has several advantages over packing: that adequate drainage of the whole wound can be combined with partial closure, so that healing occurs quicker and with less scar tissue; that secondary suture is often possible; and that, with equal comfort, the smell of the packed wound is avoided. Its drawback is that it demands constant attention and supervision, lacking which it may do harm. The method aims at bringing an antiseptic solution into contact with every part of the wound, and renewing it as soon as it ceases to be active. This object is attained by the use of the familiar Carrel tubes, lengths of soft rubber tubing ¼ in. in diameter, closed distally by a silk ligature, and perforated above this by pairs of ½-mm. holes at half-inch intervals, each pair at right angles to the previous pair. After thorough débridement a group of these tubes is laid in the wound, whose edges are then loosely approximated by a few sutures. The number and length of the tubes and the distance to which they are perforated will be governed by the need to irrigate all surfaces and recesses of the wound, and to bring the tube out through the dressings. When two or three tubes only are put in their outer ends may be left under the dressings, covered with a sterile swab but accessible for irrigation with a syringe.

When there are more than three tubes they should be connected by a glass manifold to a wide connecting tube, which in turn leads to an ampoule containing the antiseptic, and is controlled with a spring clip. The essentials of the Carrel method are a pressure of 1½ to 2 metres of fluid, large conducting tubes, very small outlet tubes, and intermittent irrigation. Under such conditions an equal amount of fluid leaves every hole in the tube system at each irrigation, and all parts of the wound are bathed and cleansed alike, but if the apparatus is joined to a continuous drip—a mistake seen too often—there is a steady trickle at low pressure that will flow along the easiest channels only, and will avoid all holes that are blocked with lymph, and all tubes leading to the deeper parts of the wound. After considerable research, Carrel selected a hypochlorite solution as the antiseptic which appeared to combine the maximum bactericidal efficiency in the presence of body fluids with the minimum damage to living tissues, and advised two-hourly irrigations because the Carrel-Dakin solution ceased to be active after this time.

With intermittent irrigation frequent change of dressings is neither necessary nor desirable. A generous covering of loosely fluffed gauze covered by abundant wool is put over the wound, and the whole limb is immobilised in some form of splint. With the recommended rate of ½ oz. of solution to every tube the amount of antiseptic and wound discharge that soaks into the dressings after each two-hourly irrigation dries up before the next and the outer wool does not become uncomfortably soaked or smelly; but a plaster cast interferes with evaporation and is apt to become sodden, so that some form of traction apparatus or Cramer's wire splinting is preferable. Irrigation is continued two-hourly day and night, and the dressing is changed only when it is uncomfortable. The tubes are left in their original positions, and are finally removed when all signs—the temperature, pulse and general well-being of the patient—indicate that infection has been overcome, and then usually after a trial period during which irrigation has been stopped.

Carrel tubes, since they are placed in every recess and wash out the discharges, satisfy very adequately the needs of wide and unrestricted drainage. Faith in the possibility of disinfecting a wound once infected, and in the value of antiseptics generally, has diminished considerably since 1918, so that few today would claim more for the Carrel technique than that it does most effectively scavenge every recess of a deep and complicated wound without disturbance to the part or the patient, or for the hypochlorite solution that it performs this service better than any bland antiseptic, or than normal or hypertonic saline. But the method combines much of the comfort and refinement of a closed wound with the safety of an open one. While it is possibly too elaborate and exacting for the treatment of war injuries, it has a definite place in normal hospital practice, where the proportion of nurses to patients is adequate and evacuation is not a pressing need. It is particularly valuable in the shearing type of injury so common in road and industrial accidents, where large areas of skin are stripped off the underlying muscles. These flaps are usually bruised and soiled with earth or machine oil, and hang by pedicles of doubtful adequacy. They cannot be cleansed with a completeness that approaches débridement, nor can they be excised or packed aside without the risk of shock and toxic absorption at the time and intractable deformity later, but they can be loosely approximated over Carrel tubes without grave risk. The method is also one of the best for treating civil compound fractures, since it involves little disturbance of the fixation apparatus, and gives earlier healing and less scar tissue than packing.

GAS GANGRENE

Gas gangrene stands apart from wound infection in general in that its cause is a particular opportunity rather than a particular organism. The causative bacteria, *Clostridium welchii* type A, *Cl. septique*, and *Cl. œdematiens* are comparatively harmless in healthy tissues, and in joints, serous membranes or subcutaneous fat cause infections that remain localised and are not particularly serious. When, however, they establish themselves in devitalised muscle, particularly in a patient whose circulation is depressed from shock or hæmorrhage, they cause a fulminating gangrene that may involve the whole limb in a few hours, and rapidly kills the patient. Gas gangrene is a clinical entity but not a specific disease, since three organisms, alone or in combination, may be responsible (see article III in this series, THE LANCET, April 20, p. 750). It is liable to appear whenever three factors coincide: first, the presence of causative anaerobes in the soil or the clothing of the injured man; second, the implantation of the organisms in a mass of muscle deprived of its blood-supply; and third, a sufficient interval between wounding and surgical treatment for the organisms to multiply, produce their toxins, and destroy further muscle by pressure. The disease has been rare in civil injuries and wars before 1914, because the devitalisation of tissues was nothing like as great as that caused by the modern high-speed projectile. It was uncommon in certain campaigns in the last war because the soil was uncultivated and free from causative organisms. It seemed to have been overcome in 1917 because the majority of the wounded were brought within a few hours to casualty clearing stations, and their wounds were excised before gangrene had appeared, but it returned in overwhelming numbers during the fighting of March, 1918, when men were often lying out for hours before they were collected, and when the exigencies of transport prevented many of them reaching a surgical unit for four or five days.

The onset of gas gangrene is unmistakable to the surgeon who has seen it before. The wounded man looks anxious, and his face is pale with a peculiar earthy pallor. Around him is a graveyard smell that is entirely characteristic; it is the smell of a corpse, and quite different from the sickly sweet stench of a stale and decomposing dressing. His skin is cold and moist, his respiration shallow, his pulse rapid and thready, his whole condition one of shock. The onset of gas gangrene in a patient already under observation is immediately suggested by a rising pulse and a complaint of pain and tightness in a dressing that was previously comfortable.

When a gas-infected limb is examined it is obviously swollen. The skin is tense and shiny, and soon acquires a mottled bronze discoloration. The swelling and discoloration may first be local, but they soon involve a whole limb segment and the parts below it. When the part is handled the crackling of gas in subcutaneous and intermuscular planes is obvious. A tympanitic note is heard on percussion, and still more characteristic is a musical hum when the skin is shaved or scratched with the finger nail. X rays will disclose gas in the tissue planes, but the method is not particularly helpful, since the discovery of gas and the diagnosis of gas gangrene are two different things. Two clinical types may be distinguished—that in which a single muscle group is affected and that in which a whole limb is involved; the distinction has no pathological significance, but it is of practical importance, since the first can be treated by myomectomy, while the second demands amputation.

The treatment is above all prophylactic. In wounds that are completely excised within the first four hours gas gangrene does not occur, and in those that are treated surgically before it is manifest it is seen only in its milder forms. When it appears in a clinically recognisable form immediate operation is necessary. Chemotherapy and specific sera should always be employed, but they do not replace surgery, since while there is gangrenous muscle there are bacteria out of reach of drugs carried in the blood-stream and manufacturing toxins in quantities liable to overwhelm the antitoxins administered. The surgical treatment of gas gangrene therefore consists of the removal of gangrenous masses, by resection of muscle groups in the limited type, by amputation if the whole limb is involved. Because tension rises rapidly in its sheath, a muscle once involved is soon killed throughout its length. The excision of muscle groups therefore means a dissection extending to the joint above, and, in removal of the limb, operations such as disarticulation of the knee which are unsound from the point of view of subsequent function are often the best for dealing with the immediate problem.

The antisera available today are far more effective than those employed at the end of the last war. Since the exact infection is in most cases unknown the polyvalent serum will be used till the organism has been isolated. There is experimental and clinical evidence that chemotherapy is also of service in gas gangrene, but not to the same extent as in coccal infections. Sulphanilamide and sulphapyridine both control experimental infections with *Cl. welchii*, sulphapyridine is more effective with *Cl. septique*, and neither has any appreciable action on *Cl. œdematiens*. The action of serum and drug is complementary, the one neutralising the toxins, the other attacking the bacteria, and they are more likely to succeed combined than singly. It is particularly important that serum should be given to those cases likely to develop gas gangrene—that is, men with lacreated wounds involving muscle who are unlikely to undergo débridement within the safe period. For declared gangrene and after operation the serum must be given in therapeutic doses. For further discussion on specific and chemotherapy in gas gangrene the reader is referred to article III, p. 750, and article V, p. 890.

SECONDARY INFECTIONS

The disinfection and mechanical cleansing of soiled wounds takes first place in war surgery, but the problem of avoiding fresh infection in a wound already made clean must not be overlooked. The risk of secondary infection can hardly be exaggerated, for whereas deaths in the army zone are due to shock, hæmorrhage and gangrene most of those at the base are due to streptococcal infection. The dangerous primary infections of war are the anaerobic spore bearers; pathogenic streptococci are not usually found in soil or clothing, and are not therefore often introduced by the missile unless it traverses the upper respiratory tract. The anaerobes can be countered, that of tetanus by specific therapy, those of gas gangrene by timely excision, but the hæmolytic streptococcus group A can establish itself even in minimal quantities and in healthy tissues. That streptococcal infection is usually secondary is suggested by the investigations of Stokes and Tytler (1918–19) who found that on admission to a C.C.S. twelve hours after wounding 12–15 per cent. of the wounded had streptococcal infections, and of Fleming and Porteous (1919) who showed that on arrival at the base the proportion was 20 per cent., and after a week at the base it had risen to 90 per cent. These infections are responsible not only for most of the late deaths but for a high incidence of septicæmia, pulmonary complications and joint infections, and therefore for much prolonged invalidism and ultimate permanent loss of function. Apart from the small number that originate in the throat of the wounded man himself the streptococci are introduced by those who care for him in transit and in hospital, from droplet infection, from unsterile instruments or dressings, or from the air while the wound is uncovered.

One safeguard which the wounded will enjoy in this war that they missed in the last is the profound scepticism of all concerned in the value of any dressing other than the first. A socratic inquiry pushed to its logical conclusion in any surgical mess would probably elicit the opinion that if a wound is excised early and well, dressed properly, immobilised properly and left

long enough in spite of the smell it will eventually heal under the first dressing. Streptococci cannot get into a sealed dressing, and after a week they can only get superficial hold in a wound whose granulation barriers are up. Much good can therefore be done by instructions that dressings are to be changed only at certain places, unless there is some indication in the general condition of the patient that all is not well.

When dressings must be changed simple precautions should avoid the worst dangers. Suitable masks, which have abolished droplet infection at operation, should be worn by all who dress the wounded. They need not be sterile and they need not be air-proof or uncomfortable, but they must be droplet-proof and big enough to exclude all spray. Hands that touch a series of infected dressings cannot be made sterile by any known means; gloves, which should be smooth and for economy may be of the thick kitchen variety, must always be worn. These gloves can be put on dry and sterilised on the hands between dressings by washing them with soap and hot water and then dipping them for one minute in 2 per cent. lysol. Dressings and instruments are probably sterile at the start of a day's round, but it must be remembered that streptococci abound in the air and dust of a ward where infected cases lie, and can easily gain access to the dressing tray. The tongs kept in a jar of lysol for taking instruments in and out of bowls, and the pair of dissecting forceps standing in spirit and used on several dressings before they are re-boiled are obvious sources of contamination. It may be wise to segregate cases of streptococcal infection, and it is certainly advisable, in all but the most advanced units, that patients should be wheeled for dressings to a side room where much of the technique of the operating theatre can be practised, but the cases that really do need dressing on any one day should never be many.

THE PART OF CHEMOTHERAPY

Upon the success of such simple measures to eliminate streptococcal infections will depend to some extent the part that sulphanilamide comes to play in the treatment of wound infections. That this and allied drugs have the power to combat an established infection, and a still more remarkable power if administered shortly before the entry of infection to prevent its establishment, may be taken for granted.

The aim of prophylaxis, as set out by Fuller and James (1940) is to obtain a blood concentration of 2 mg. sulphanilamide per 100 c.cm., and to maintain it at this level during the danger period, in practice for four days. To ensure this concentration a first dose of 1·5 g. of sulphanilamide (3 crushed tablets) is given in 100 c.cm. of hot 1 per cent. citric-acid solution, to ensure rapid absorption. A single tablet (0·5 g.) is give whole two hours later, and after that one tablet four-hourly to the end of the fourth day. After twenty-four hours 2 tablets may be given eight-hourly if this is more convenient. Thus 13·5 g. in all is administered in the four days.

There is abundant evidence that chemoprophylaxis is more certain and requires smaller doses than chemotherapy. On these grounds the case for administration of sulphanilamide to every wounded man appears convincing. The fear that the drug might aggravate to a dangerous degree the collapse of a patient already shocked seems to be belied by the experience of American surgeons in the treatment of severe automobile accidents. The only practical objection to the routine use of sulphanilamide is the doubt whether primary streptococcal infections are sufficiently common to justify a course that may add to the difficulties of administration in the forward areas and to the cost of the medical services.

The place of chemotherapy in the treatment of established streptococcal infections is too well recognised to need elaboration. The slightest suggestion in the way of increased pain, temperature or pulse that anything is amiss with a wound that has been excised will be the indication for the immediate culture, and the administration of three 1 g. doses of sulphanilamide in citric acid at hourly intervals pending a bacteriological report.

The use of sulphanilamide as a local application in wounds after débridement is on trial, but it can be said already that the practice has no obvious disadvantages and much to recommend it. The drug is placed where it will have the greatest action on any bacteria that have escaped mechanical removal, it appears to do no harm to the wound surfaces or to phagocytes in the neighbourhood, and it is absorbed and continues to act through the circulation. The view expressed by Buttle in article V of this series that not more than 15 g. should be used in the dressing to avoid the risk of toxic symptoms from absorption, and that in the presence of clinical infection oral administration should be started after forty-eight hours, by which time the drug absorbed from the wound has been largely eliminated, should be borne in mind.

Sulphanilamide is recommended as a local application in recent wounds only. It has been suggested that a cylinder of the drug should be inserted on the field at the time of the first dressing and this may prove an effective and the simplest form of prophylaxis. In hospital its value is as a coating on a surface that has just been cleansed by surgical excision; it can do little good in the presence of gross contamination and much damaged tissue, and in established infection it is less effective locally than when given by mouth. The safety of an open wound and the danger of a closed one are so well known, that it may be wise, till further experience has been obtained, to pack wounds over the sulphanilamide unless they belong to the small group that would in any case be considered suitable for primary suture. If, however, the first trials indicate that infection is overcome in the majority of wounds so treated, trial will be made of primary closure over the sulphanilamide, first with deep simple wounds, then with through and through tracks, and finally with gunshot fractures. The gain would be on the one hand a more effective action of the drug and on the other a saving of time and a better functional result. It will almost certainly be advisable to pass from local to oral medication after the second day, and to continue till all signs indicate that clean healing has, in fact, been obtained.

(To be concluded)

The Lancet 100 Years Ago

May 23, 1840, *p.* 319.

From a letter to the editor.

Terrible as the death of Lord William Russell has been, by the hand of the ruthless assassin, that amiable nobleman narrowly escaped a much more painful and scarcely less horrible termination of his life, during his last visit to the Continent. His lordship, who had been long afflicted with a great defect in his hearing, happened to be at Paris when the new method occasionally adopted for the removal of that infirmity by the introduction of an instrument through the nostrils, and forcing it into the passage leading to the ear, was the topic of general conversation. Being very desirous, if possible, to be released from his distressing deafness, his Lordship applied to a resident eminent surgeon, conversant with that mode of treatment, who declared the case to be fitted for, and strongly recommended, the novel practice, which he assured his noble patient was an easy and efficient remedy for instances of a similar description. Lord William informed the writer that, prevailed upon at length to submit to the operation, had he been aware of its severity, he would sooner have perished than endured the agony it inflicted,—that the sufferings consequent on its performance lasted, with great intensity, for several days, during which he was in momentary danger and expectation of suffocation, and, what was worse, after all, not the slightest benefit was afforded to the disease, for the promised relief of which the operation had been undertaken.

SPECIAL ARTICLES

ANXIETY AND THE HEART

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ACCORDING to the Oxford Dictionary, anxiety has acquired a special meaning as a medical term—namely, "a condition of agitation and depression with a sensation of tightness and distress in the precordial region." The singling out of a colloquial word as a medical term is the more remarkable because there is a choice of other words describing psychological states with a similar emotional background—e.g., apprehension, alarm, anguish, fear, fright, dread, agony, terror and panic. These words differ one from another in meaning partly in the degree of the affect described, partly in the time-relation between the affect and its cause (the danger), and partly in the type of motor reaction combined with the affect. Anxiety differs from all other members of the group in not implying any particular degree of affect. "It varies greatly from, on the one extreme, a slight abashment, awkwardness, embarrassment or confusion, to, on the other, a degree of indescribable dread that may even rob the sufferer of consciousness" (E. Jones). Anxiety has no relation to any definite danger, object or event, and has therefore been defined as "fear without object." Consequently anxiety is not accompanied by characteristic protective movements, such as running away in fear or panic and cataplexy in terror.

Anxiety is further distinguished from the last-mentioned states by the sensory element which is an integral feature of it. These sensations, which lend themselves so easily to description in terms of symptoms, have certainly helped the word "anxiety" to its favoured position in psychological medicine. The "Dictionary of Psychological Medicine," by Hack Tuke (1892), already gives the definition quoted above; but in Walsh's "Psychotherapy" (1912) the word "anxiety" is not used and the appropriate facts are set out under "Dreads." Walsh thus avoids the confusion which is so easily produced by the broader colloquial meaning of the word "anxious"—i.e., "troubled in mind about some uncertain event, or being in disturbing suspense" (Oxford Dictionary). Anxiety in this sense is related to an indefinite object and contains very little, if anything, of the characteristic emotional background which ranges the medical term with fear and similar affects. Everybody who knows the confusion in terminology of our subject will agree that a discussion on the definition of anxiety is necessary for a proper description of the facts.

SENSATIONS EXPERIENCED IN ANXIETY

Observation shows that, in anxiety, besides the precordial oppression, which is perhaps the most important sensation, other sensations arise, such as dimming of vision, shortness of breath, weakness of the knees, giddiness, tension in the head and pressure in the abdomen. Any one of these may dominate the symptoms in any particular case and may even overshadow the precordial sensations. The sensations can be understood by considering the ordinary physical accompaniments of anxiety. These are, besides increase of heart beat and rise of blood-pressure, frequent and deepened respiration, pallor, sweating, cessation of salivation, increased peristalsis, desire to micturate, and tremor or loss of tone in the voluntary muscles. The principal humoral changes are mobilisation of sugar from the reserves of the liver and the secretion of adrenine from the suprarenal medulla. Cannon has summed up all the factors of this complex reaction as preparatory "for running away in order to escape from danger." From clinical observations it seems proper to apply to human anxiety this teleological interpretation originally intended to explain the accompaniments of fear in animals. Cannon has also shown that the physical accompaniments of anger are very like those of fear, a fact not unimportant in the diagnosis of an attack of anxiety from physical signs only or from their description by the patient. Blending of anxiety with anger and rapid alternation between fear and rage may take place in normal persons but are especially common in neurotics. Blending is facilitated by the identical set of accompaniments.

The whole of the anxiety reaction is integrated by the vegetative-endocrine system, and it can be set going by any of its components, mental or physical. Recollection of a past terrifying experience may release it from the mental side; it may, on the other hand, be produced by an attack of paroxysmal tachycardia. Respiratory embarrassment in an attack of asthma, vestibular stimulation in a descending lift, and sudden vasoconstriction with consequent rise of blood-pressure after administration of adrenaline or of cocaine are further examples; a sudden fall of blood-pressure in fainting can have the same effect.

As regards the subjective sensory experiences characterising anxiety, there is no doubt that, from the medical point of view, the precordial sensations are by far the most important. L. Braun, from his observations in patients with angina, even holds the opinion that anxiety is a specific sensation of a special organ, the heart. However, the subjective experience of cardiac disease cannot be understood in the light of these sensations alone; they must be viewed against the background of popular ideas about the significance of the heart in human life. Although such ideas belong to common knowledge, it seems worth while to review them briefly.

SYMBOLIC VALUE OF THE HEART

The heart is regarded as the most vital part of the body; the end of its beating means the end of life. Its rhythm, propagated by the blood-stream, can be felt everywhere in the body. The blood is the carrier of life; loss of blood means menace to life. Although many organs and functions of the organism have their own rhythm, one is always inclined to relate all vital rhythm to the pulse-rate. In many languages heart is synonymous with soul, vital centres and the seat of the emotions and affection. History shows that this significance of the heart is not derived from the modern knowledge of its functions. Already for the ancients the heart was the seat of the soul and of the predominant emotions. Similar views have been held by many races in all ages. This concordance of opinion points to a common origin, which we are inclined to trace to the sensations common to all, connected with emotions. The normal heart beat at rest is imperceptible. Every variation in the psychological field—e.g., concentration, effort and intellectual activity—is accompanied by changes in the heart-rate, but these are most pronounced and most noticeable when associated with emotions. They tend to become conscious sensations in all emotions which do not lead to immediate activity. These normal sensations are localised in the cardiac region and not referred to another part of the body. Whenever the heart beat enters consciousness, it either confirms the awareness of life or signals danger and produces anxiety. Subjective sensations and their popular elaboration, however, cannot in themselves fully explain the popular significance of the heart. There must be some common urge to centralise or to symbolise the life of the individual in one organ. Diaphragm, solar plexus and pineal body have served their turn, and mental inertia keeps such beliefs going,

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even if their scientific or philosophical basis has gone out of fashion.

SYMPTOMS IN HEART-DISEASE

Another contribution to the idea of the vital importance of the organ comes from the subjective experience in heart-disease. It is generally agreed that sensations are of little use as a diagnostic guide in organic heart-disease. Textbooks emphasise that in cardiac illness symptoms may or may not be present. Variable as the local sensations may be, if they reach a certain intensity they tend to produce feelings of impending death. Coarse disturbances of rhythm are in many cases not perceived at all, whereas in other patients unpleasant sensations may be present without much pathological significance. Fahrenkamp showed statistically an inverse correlation between subjective complaints, especially palpitations and objective findings in the heart. However, it would be a mistake to assume that organic heart-disease prevents the patient from developing neurotic symptoms related to the same organ—a rule which holds true for many other organs of the body.

The starting-point of every psychological approach to "heart neurosis" ("functional debility of the heart," "disordered action of the heart") must be the patient's perception and self-observation of the cardiac region and action. There are several ways in which this may become the centre of a neurosis :—

(1) The simplest way is by a sudden emotional shock—e.g., anxiety during a traffic accident—in which the stronger action of the heart is perceived and becomes the predominant complaint. Normally it disappears with the emotion after a short time, but in special circumstances, such as compensation wishes, unemployment, and other critical situations, it may become a fixed pattern of behaviour comparable to a conditional reflex, ready to reappear under any emotional demand—e.g., a medical examination. Unusual physical exertion or exertion under emotional strain may be a cause. Sexual excitement, for instance, has a pattern of physical accompaniments very like that of anxiety; hence, if a neurosis-producing psychological conflict is associated with the sexual act, the clinical picture is easily converted into that of cardiac neurosis.

(2) In chronic emotional stress—e.g., business difficulties, marriage conflict and overbearing responsibilities—cardiac action can adapt itself to a large extent. The moment, however, that the patient thinks his situation unbearable, or even if he only becomes afraid of this eventuality, anxiety sets in, bringing the newly strengthened cardiac action above the threshold of consciousness. If the person takes refuge in illness as a way out of his difficulties, the attention once drawn to the cardiac sensations remains fixed and a "heart neurosis" ensues.

(3) A similar development may take place where there is already an abnormal psychological state, neurotic or psychotic—e.g., a depression or an obsessional illness—producing high emotional fluctuations with corresponding strain on the heart. For some reason or other, attention may be directed to the heart and the clinical picture be modified by cardiac symptoms, which often first lead the patient to consult a doctor.

(4) There are two types of abnormal personality especially inclined to "heart neurosis": (*a*) sensitive persons ("psychathenics") liable to emotional upsets which render them limp and devoid of all energy; they are worried by trifles and are plunged into a state of anxiety on the slightest provocation; an abnormally responsive circulatory system is constitutional in many such patients, and this favours, from the bodily side, their neurotic concern with the heart; and (*b*) the other type—in some respects the opposite of the former—composed of people who crave for emotions. They like a high pitch of affect and are constantly on the look-out for something sensational and exciting. They always find something to kindle their emotional fire. Such an attitude must be a considerable strain on the cardiac action. "Highly strung" persons of this kind are often inclined to symptoms of "conversion hysteria," and it is easily understandable that in these people such symptoms are usually referred to the heart.

(5) Popular views about the symbolic significance of the heart, as described above, may be an important determining factor in any of the cases enumerated in the former paragraphs. In some instances they can be regarded as the sole factor responsible for the choice of the organ on which the neurotic fixes his complaints, the more so if the views are underlined by an authoritative medical opinion. The student is warned against this danger in all textbooks, and the mere fact that this warning is so often repeated shows that it is still not observed as it should be. One has to guard against this danger not only in patients without morbid physical signs but also in organic heart disease. Heart patients are very liable to keep an anxious watch on their cardiac action. Extrasystoles, paroxysmal tachycardia, and slight anginal symptoms are apt to aggravate their anxiety, causing an additional strain on the circulation and leading to a vicious circle.

There is still much work to be done in relating the subjective experiences of different cardiac disturbances to the psychological make-up of the patient. Much can be said in favour of giving up the concept of cardiac neurosis and organ neurosis in general and describing instead each case as the response of a personality in the light of its heredity, character, and environment. This would emphasise the importance of the psychological approach in addition to the pathophysiological.

MEDICINE AND THE LAW

No Compensation for Workman's Sunstroke

SITTING with a medical assessor at Wellington, the county-court judge refused to award compensation to a postman who had an attack of giddiness after walking up hill in the sun on a hot day in August. According to the brief report in the *Solicitors' Journal* the applicant had served 25 years in the army and then 3 years with the Post Office, losing only a few half-days through illness. After the attack of giddiness there were symptoms of paralysis. Massage and electrical treatment were administered to the left arm and leg. The postman was afterwards retired on grounds of health with a gratuity of £55. He claimed compensation for the partial disability following the incident in August. The court heard medical witnesses on both sides and decided that the postman had not discharged the onus of proof that his incapacity resulted from his employment.

These questions of injury by the forces of nature—e.g., sunstroke or lightning cases—were examined afresh this year by the House of Lords in Dover Navigation Co. *v.* Craig, where a seaman died of yellow fever contracted during a voyage to a West African port. "If," said the House of Lords, "a workman, while on his employment, is accidentally injured by a force of nature which is operating generally in the area where he is, he cannot recover unless he can show that his employment exposed him in a degree beyond other people then present in the area to the injurious effects of the natural force." The claim in Craig's case succeeded because his work as a seaman took him into the dangerous place. The House of Lords was invited by counsel to imagine the case of a seaman sent to a British port where influenza was rife. Would he have a claim under the Workmen's Compensation Act if he caught the prevailing epidemic? True to the judicial tradition of answering one question at a time, the judges "smiling put the question by." Logically, it would seem, they might have answered the influenza problem in the affirmative. So also with the postman. The sun was hot for everyone on that hillside in Somerset in August, just as the mosquitoes were ready to bite everyone

in that West African river. The seaman's work took him to the river and the mosquitoes bit him; he died and compensation was awarded. The postman's work took him up that hill in the sun and he ascribed his illness to the effects of the sun. There must have been some weak link in his evidence. If he could sufficiently have shown that the sun caused the attack of giddiness, ought he not to have obtained his compensation? Does it matter that somebody else on the same hillside on the same day did not feel the sun or that somebody else on the West African river was not infected with yellow fever?

IN ENGLAND NOW

A running commentary from our Peripatetic Correspondents

IN time of war many of the stately homes of England see strange sights. To their new functions they bring their old retainers, and of the hybrid collection inherited by our hospital no-one has afforded more entertainment than "Flannel-feet," the fireman. He was at one time a fireman in his native Lancashire, but left it for a more salubrious clime nigh on twenty years ago. Flannel-feet is not his real name—that, oddly enough, was Burner or "Mr. Burner to you" as he is wont to say on his uppish nights—but the name seemed to suit him as he prowled along our ill-starred corridors, and Flannel-feet it has remained. If the risk of fire is serious in a mansion it assumes added importance when that mansion becomes a hospital, and Flannel-feet was quick to appreciate that he had entered on an enhanced sphere of usefulness. He needed little persuasion to show parties of staff his system of fire control and the gadgets to that end and it was with a lively sense of adventure ahead that eight of us set out in his wake to see the sights.

It was important, our guide explained, to begin at the commencement, and we were taken to the front hall to see a collection of bells and buzzers noisy enough to waken the dead. This was the alarm board, and from its mysteries we went on to explore emergency exits, to learn why it was that in the event of fire patients could not be evacuated through ground-floor windows, and to be initiated into the working of hoses and fire extinguishers. The emergency exits were straightforward enough, but it appeared that in the more palatial days it had been found necessary to seal permanently all ground-floor windows, not from any desire to exclude fresh air or burglars but because unruly members of the staff used these windows to regain the sanctuary of the building when the day was far spent. On one unhappy occasion a servant had actually been known to come through one of the ground-floor bedrooms when it was occupied by a lady guest; the enormity of his offence was not that he had done so but that when doing so he had smoked a cigarette. Fire hoses, it appears, have many uses. Sometimes guests have taken them away to water their gardens, even twenty-five yards of hose, though that must have occupied a fair-sized hat box.

As the tour proceeded certain members of the party began to exhibit a spirit of levity and Mr. Burner did not at all approve of this turn of events. He seized the opportunity afforded by his demonstration of fire extinguishers to let a weapon of heavy type fall on the feet of one of the less responsible surgeons, muttering by way of comfort, "There, you've missed it," though it had obviously been dropped in such a way as to offer little prospect of any other outcome. "When you first suspects fire you do not ring the fire bell. You sniffs for smoke and you tries to put it out. Then you gets the 'ousemaid on the floor."

Flannel-feet was not to be satisfied with any mere tour of the building, however profusely illustrated, and nothing would do but that we should foregather on the morrow to see a practical demonstration of fire-fighting, including instruction in how to cope with an incendiary bomb. The bomb refused to play the game. It consisted of a small mountain of debris reputed to have been doused with precious petrol but it proved to be rather a damp squib and the mass took some persuasion to light at all. The resultant fire was not very formidable, but was not extinguished without some little horseplay. Then we were led to an upper corridor to learn how to cope with a real fire. Two volunteer victims were stowed away at the site of battle and the members of the emergency fire brigade sent about their normal business with strict injunctions to listen for the whistle and be sure to bring something to the fire. Bringing something to the fire is apparently the secret of successful fire-fighting: "the fire brigade does not go to a fire without its hengine." The stage was set, the whistle blown and after a discreet interval the hired assassins came scrambling along the corridor with a weird collection of pails, shovels, hammers and fire extinguishers, for even in these matters the world is ill-divided. The room that housed the victims was pointed out, the door thrown open and in crawled the rescuers to return with two sack-like creatures obviously trying to make themselves as limp and heavy as possible; the response to artificial respiration was brisk.

Flannel-feet is a reminiscent soul, He thinks of everything, and especially do his thoughts linger in the glorious past. When he heard that we were to have our first concert he thought it would be necessary to have a "chooker-out," though surely such a thing or such an expression would be unknown in the palmy days of our stately home, unless indeed the unruly staff had been wont to mingle with the mighty. And yet, perhaps not, for it appears that even in these days there were events reminiscent of boat-race night. On one occasion when 'Enery 'All's band had been leading the praise the "kettle-droom" disappeared in some mysterious way. Great was the consternation and great the searching—in which Flannel-feet played a surreptitious but ineffective part—until at last the drum was run to earth in Edinburgh of all places, having been passed through a billiard-room window to the car of a souvenir-hunter outside. It might have been lost for good but for the vigilance of a bright young page-boy who had noted its nefarious transfer to a car and carefully noted the car's number.

Flannel-feet will remain one of the happy recollections of our strange adventure, a man believing in the importance of his job and anxious to make the most of it, yet possessed of the saving grace of humour. Perhaps most valuable of all in circumstances such as ours, a man willing to lend his hand to whatever came and able to get on with the job.

* * *

Not being used to it, general practitioners are often unskilled in the use of leisure. The very nature of their work, with its uncertainties and interruptions, tends to produce a state of restlessness and inability to settle to anything. This is further aggravated by these troubled times wherein it is doubly hard to come by and retain a quiet mind. Barely two miles from my home there runs a small stream, not much more than a brook, which is heavily overgrown and far too muddy. It is, however, a nice long way from civilisation, and, what is more, holds a few little trout. These run perhaps three to the pound—assuming that the two you don't catch are rather larger than the one you do—but they are game and wary little fish. Sometimes on a fine evening after the sun has left the water I sneak away to my brook clad in an old coat, a disreputable pair of grey bags with a "shirt hernia," and gum boots. I crawl along the banks, among the docks and nettles, and flick—you can hardly call it cast—a march brown and a blue upright into the likely pools and stickles. More often

than not I "hang up" in a tree or bush and have to climb about like a schoolboy to unhitch my cast; very occasionally I am rewarded with a little trout. An hour or two of this sort of thing produces a feeling of honest fatigue and peace that I find singularly satisfying.

* * *

The summer exhibition at the Royal Academy shows evidence of a return to the nude. In the oil paintings the drawing is, in the main, anatomically correct, though for some reason the lower limb, when extended, is often made too long. We see this in the left of the three "Sirens" (177) of Mr. W. G. de Glehn and again in the young lady who is "Reading Goldoni" (205) by Mr. John B. Souter. Our artists are still using their grandmother's figures for their models. Thirty years ago we were taught that of the anatomical differences between the male and female body an important one was that the woman had a thicker layer of fat under her skin and that this prevented the individual muscles being seen beneath it. This we know to be incorrect now that young women take as hard muscular exercise as do men. Yet with one exception all these nudes are painted from figures which retain the covering of adipose tissue, sometimes considerable, that comes from want of exercise. The result is seen in the drawing of the forearms. In Miss Ethel Gabain's "The Little Dancer" (656) the head and figure lean forward full of activity, but the forearms are flat and devoid of it. So experienced a painter as Mrs. Dod Procter in her "Smiling Girl" (90) shows a vivid head and neck with a pair of truncated cones as forearms. The exception is Mr. Harold Williamson's "June Morning" (171). His Portia putting up her hair with her hands above her head is the virile young woman of today. Our artists would do well, I think, to turn from the texture and the tone of the skin to the ripple of the muscles under it. Of this there is one example in the nearly nude figure that the modern bathing suit provides (368). Again it is Mr. Harold Williamson. A young woman, seen from the back, is sitting by a pool on a rock. A wave has splashed up some spray and the figure leans backwards, holding up her arms, with open hands, to protect her face. The deltoids are beautifully depicted, and behind them the other muscles of the shoulder girdle are seen in play.

It seems questionable whether, except as a part of the practice and study of an artist's technique, there is now any room for nudity in art. The settings of the nude have changed from those of religion and mythology to scenes of everyday life, and thereby have lost all reality. Do young women really take off their pyjamas on arising from their couch before they comb their hair (171), or sit unclothed in the middle of a room with open windows through which suburban neighbours can get a full view (322)? I am quite certain that three young women (732) do not get out of a punt to lie or sit, stark naked except for one pair of shoes between the three, on a river's bank just by a lock through which a barge might come at any moment. The lock-keeper's wife would soon be after them. It is this unreality which divorces modern art from the people. These have "a sense of immortality" as much as have the well-to-do, and they know more of the "opposition to mere necessity and chance"; but you must take the art to the people as the wireless has done with music; and it must be, in the main, of home and homely. It has been done before and there are signs in this exhibition that it can be done again and done well.

Anyone who saw the late Earl of Crawford and Balcarres, even if he did not know him, can recognise in Mr. James Gunn's study (739) a good portrait as well as a good picture. It is a pity that the same cannot be said of that of The late Prof. Edward Mapother (294) by Mr. Alfred R. Thomson. However good this may or may not be technically it is meaningless as a remembrance of a great little man. The expression is flat, and Mapother's was never that. It contains none of the vitality that was always in his face, none of the force that changed the lives of men that came in contact with him, none of the zeal, almost fanatical, for his chosen work. Above all it has missed the struggle against illness with which he carried on, and which for years made his life heroic. Then there is the portrait of Sir Joseph Barcroft which Mr. R. G. Eves has deposited as his diploma work. It has caught him to the life—perky and alive. Best of all, in the opinion of an amateur in art, is that of Sir Robert Hutchison by Mr. James Gunn. Here is quiet meditation, with a humour in the eyes and in the folds around the mouth. There is a kindliness with a firmness of purpose seen in the hands as well as in the face which make this my choice as the best portrait in this year's academy.

SCOTLAND

(FROM OUR OWN CORRESPONDENT)

RESTRICTIONS ON ALIENS

THE Government decision to intern German and Austrian citizens has had evident effects in Scottish universities and hospitals. A considerable number of alien doctors have been in Edinburgh studying for the qualification of the Scottish Conjoint Board. Their internment will be a serious blow to them, since their financial resources are limited. The order also affects the students and recent graduates of the university who came to this country in order to start their medical course at the beginning. Some of these young graduates have been permitted to take house-appointments on condition that they were not engaged in the treatment of soldiers or civilian air-raid casualties. Their sudden internment will seriously inconvenience their hospitals, although it is, of course, in the national interest. The restriction of aliens applies to non-enemy as well as enemy aliens, and many American undergraduates are now prohibited from being out of doors after 8 P.M. Representations are being made on their behalf to the local police authorities for some amendment of the "curfew" hours, partly on the plea that their freedom of movement at night is necessary for their attendance at emergency work in the hospital. So far as Edinburgh is concerned some 50 or 60 Americans attending the school of medicine of the Royal Colleges are affected.

HOSPITAL SUPPLIES AND NURSES

The Department of Health for Scotland is urging on hospital authorities the necessity for the strictest economy in hospital supplies and in particular in consumable materials. It has become increasingly difficult under war-time conditions to obtain medical and surgical equipment since many of the raw materials are imported from abroad. The conservation of shipping space and of foreign exchange also makes a reduction in the importation of these materials desirable. Among the items detailed are cotton wool, gauze, lint, mackintosh sheeting, quinine, cascara, and castor oil. It is hoped that as far as possible damaged articles will be repaired rather than replaced. Appeals are still being made for nurses and nursing auxiliaries for the emergency hospitals in Scotland, and the Secretary of State has asked all members of the Civil Nursing Reserve to fulfil their undertaking to serve in the emergency hospitals whenever they are called upon. The most urgent need is for full-time staff. Many who have been trained as nursing auxiliaries are in other employment and are prepared to offer full-time service if they can be assured that their jobs would be open to them when they return. The Secretary of State has appealed strongly to employers to release such nurses and auxiliaries as far as possible with an undertaking that their employment will be available to them when they are no longer needed in the hospitals.

OBITUARY

LOUIS BATHE RAWLING

M.B. CAMB., F.R.C.S.

Louis Bathe Rawling, who died on May 10, was educated at Clifton and Caius College, Cambridge. When he came up to St. Bartholomew's Hospital in the 'nineties he quickly won a popularity which was to accompany him throughout his long life there. A contemporary remembers him as a thin, tall man of rather nervous habit which earned for him the nickname "Jumpy," which stuck. He qualified in 1896 and took his M.B. the following year, when he was awarded the Brackenbury surgical scholarship. He was house-surgeon to Alfred Willett and Harrison Cripps, and he won his spurs as a teacher of surgical anatomy while he held the post of demonstrator at the hospital. There too he wrote his book, "Landmarks and Surface Markings of the Human Body," which has been translated into many languages and is familiar to many generations of students. In 1900 he obtained his F.R.C.S. and two years later he was runner-up for the Jacksonian prize with an essay on fractures of the skull. This decided for him the direction of his work and he determined to specialise in cranial surgery. In the years that followed he was three times appointed Hunterian professor, he became a member of the court of examiners of the Royal College of Surgeons and in 1904 he was elected to the staff at Bart's. He was appointed full surgeon in 1919. Of his work there a colleague writes: Few men have lived more useful lives, for to few has been given a larger measure of confidence in his transparent honesty of purpose and the quiet determination with which he pursued the course to which his mature consideration had led him. No man ever had a more genuine colleague in the best sense of that term, and no colleague ever failed to trust him completely. By each of these he will be remembered as one who in Dr. Johnson's phrase "gladdened life."

During the last war Rawling held the rank of major in the R.A.M.C. He commanded the surgical division of the 34th General Hospital and later served on the staff of the 1st and 4th London General Hospitals, and in India. On his return to civilian practice he was appointed surgeon to the West End Hospital for Nervous Diseases. He was married and had two daughters.

Sir D'Arcy Power writes: I knew Louis Bathe Rawling from his early student days when he had just come down from Cambridge to begin his clinical work at St. Bartholomew's Hospital. For some years he was my assistant surgeon, at that somewhat remote period when it was the duty and the pleasure of the assistant surgeon to attend and help his surgeon in the operating-theatre. Tall, good-looking, debonair, of a cheerful countenance and a gentleman, he always met me with a pleasant word and a smile and we never had a misunderstanding during the whole time we worked together. There was an intermediate period when he was a house-surgeon. It was then the duty of C. B. Lockwood and myself, as the two junior assistant surgeons, to supervise the house-surgeons every morning at nine o'clock in the casualty department of the hospital. Rawling never had to be reported for he was never a minute late; he treated the vast hordes of outpatients as human beings and was always on friendly terms with his "dressers." He was somewhat oversensitive because being in the ordinary course assistant surgeon to Lockwood, my immediate senior, he degraded and attached himself to me on the ground that he was not good at repartee. He retired from practice soon after he had become the senior surgeon to the hospital which was the goal of his ambition. When I saw him a few months ago he was as cheerful as usual and said that he was living quietly and happily near Exmouth.

One of his former house-surgeons writes: Although our old chief retired from active practice in 1932, he kept in touch with all of his house-surgeons through the Rawling club, which was founded some fifteen years ago. This club met once every year, when the chief, the assistant surgeon, the chief assistants and all the past and present house-surgeons dined together, and talked over old times. Mr. Rawling had this club very much at heart, and he expressed the wish that it should be carried on as a "Firm" institution when he should be no more. It was always a great pleasure to meet him again, to be greeted by that cheery smile, and to hear his "Well, me lad, how are you?" He combined a kindly and courteous personality with a shrewd clinical acumen, and as a surgeon he was particularly deft and gentle with his hands. In spite of his exalted position in the realm of surgery he was singularly modest, and his nature had no room for jealousy.

GEORGE WILLIAM SHORE

O.B.E., M.D. LOND., D.P.M., COLONEL, R.A.M.C.

Colonel G. W. Shore died in Charing Cross Hospital on May 8, a few hours after being taken ill while travelling on the Underground. He was born in 1888 and educated at Dulwich College and King's College Hospital, where he qualified in 1911. After holding resident appointments at King's he took his M.B. in 1914 and was then appointed Sambrooke medical registrar at the hospital. But at the outbreak of war he left to join the R.A.M.C., in which he served for five and a half years. Much of this time he spent in Mesopotamia as ophthalmic surgeon at No. 40 British General Hospital. He was invalided home and was afterwards appointed assistant registrar and later registrar at the 4th London General Hospital. He also acted as ophthalmic specialist on the War Office medical board and as military representative on the Ministry of Pensions boards. He now had leisure to continue his postgraduate studies, and he took the D.P.H. in 1921 and his M.D. and D.P.M. in the next two years. He was then appointed assistant medical officer at Springfield Mental Hospital, and later he also became a lecturer in mental diseases to the Westminster Hospital, where he held a clinic for early mental disorder. In 1933 he was appointed medical superintendent at the new mental hospital at Shenley. Here his capacity for organisation and his administrative talents stood him in good stead. Meticulous and conscientious, nothing was ever too much trouble for him. He made apparently trivial details which yet affected the welfare of the patients his immediate and personal concern. When war was declared in September part of the hospital was taken over by the military authorities, and as a lieutenant-colonel in the Territorial Army reserve of officers Shore assumed command. Later he was promoted to colonel.

Lafayette

Shore radiated kindliness and sympathy. His humanity and bigheartedness were implicit in every contact with his staff and his patients. Much of the leisure of his busy life was devoted to music. A friend describes him as a delightful colleague, a charming host and an able physician.

VIOLET KELYNACK

M.B. EDIN.

Mrs. Kelynack was born in Calcutta, the daughter of James Grieve McLaren. She was educated at Bedford High School and went on to study medicine at Edinburgh University as a member of the Scottish Association for the Medical Education of Women. This association had been established to secure for women the medical lectures given by extramural lecturers, for only two of the university classes—physics and zoology—were then open to them. In those days women students laboured under a great disadvantage, for special lectures were sometimes difficult to obtain and laboratory facilities were inadequate. In spite of these obstacles Mrs. Kelynack was one of those who in 1903 obtained the degree of M.B. A contemporary recalls that she would often join the rebels in seeking to get the university facilities opened to women, an object which was however not obtained until 1916. To the end of her life she remained a great lecturer on equality of opportunity and pay for medical women and was eager that women should play their full part in world politics. In these early Edinburgh days she was already interested in poor children and she did much work at the Cowgate Mission. After graduation she was for a time a clinical assistant at the Evelina Hospital in London, but she did not long practise her profession for soon afterwards she married Dr. T. N. Kelynack. For a while they lived in Manchester and then moved to Mount Vernon Sanatorium where her husband was appointed medical officer.

Vandyk

From her home at Harpenden she undertook much useful work, principally among children. She was honorary medical inspector for girls at the St. George's Coeducational School, assistant medical adviser to the National Children's Home and Orphanage, and assistant medical officer to the children's sanatorium there. But in 1921 she became medical secretary to the Medical Women's Federation and for the rest of her life she gave her time, thought, and energy to its interests. During its early years when the federation was emerging as an embryo association whose special job was caring for the interests of medical women in all parts of the world it owed much to her skill and guidance. Her contacts with other medical associations and people gave her a wide vision and her organising ability was supported by her tact and courtesy. Almost the last thing she did before she gave up her work on account of ill health in March was to supervise the publication of the current issue of the federation's quarterly journal which she edited. A friend describes her as "a quiet and somewhat unassuming personality but tenacious of her opinions, who would take a strong stand on controversial questions once she decided it was right." Her only daughter is also a medical woman.

Dr. Catherine Chisholm, a former president of the federation, writes: Mrs. Kelynack made the London office of the federation a pleasant centre where medical women, especially those up from the provinces, met a friendly welcome, received every assistance and were at once put into touch with the sources of any information they required. During the time when I was president of the federation, in particular, I realised her tactfulness, her quiet efficiency and her knowledge of all that was going on. She was always ready to take any amount of trouble to ensure the smooth running of the organisation both within and among its own members and in association with other bodies. Our meetings in London and in the provinces have been models of accuracy. Whoever else got ruffled Mrs. Kelynack and her assistants never did. Mrs. Kelynack was so retiring and quiet that it was not so easy to realise how much she was doing and how quietly she was making wise suggestions. I have been impressed by the recognition of her kindness to the younger members of the council coming up for the first time to the meetings. This has been expressed to me by those who have rung me up on seeing the notice of her death. Though latterly she was often suffering physical disability she always remained cheerful and uncomplaining. The debt owed to her by the federation cannot easily be estimated and all those who have worked with her will remember her with gratitude.

CHRISTOPHER KILVINTON MOWLL

M.R.C.S.

Dr. C. K. Mowll, who died in London on May 15, aged 47, was the third son of the late Henry Martyn Mowll of Chaldercot, Dover. He was educated at the King's School, Canterbury, the University of Cambridge, and the London Hospital. He qualified in 1917, and during the last war served in Mesopotamia. In 1921 he joined the headquarters medical staff of the Post Office, where he remained till 1937 when he was appointed chief medical officer to the Southern Railway. Mowll was deeply interested in Sunday-school and missionary work, and was known to many people as a lay preacher.

H. H. B. writes: "Mowll was a man of big physique, with a deep sense of duty, and strongly held, almost fundamentalist, theological views. But his personal religion was a thing apart from these and the mainspring of all his actions. It would have been impossible to imagine him doing a mean or self-seeking thing, however small, or to believe that anybody who wanted help from him ever went in vain."

ALEXANDER GARDNER ROBB

M.B. R.U.I., D.P.H.

THE death of Dr. Robb on May 6 has removed from the Belfast medical school an outstanding and well-loved figure. He was born in 1866, the eldest son of the Rev. James Gardner Robb, of the Irish Presbyterian Church. Two of his brothers, Lieut.-Colonel J. J. Robb and Captain J. Campbell Robb, are also doctors, while a third, Mr. J. H. Robb, is minister of education for Northern Ireland.

Alexander Gardner Robb qualified as M.B. from Queen's College, Belfast, in 1891, and obtained the D.P.H. of the Royal College of Surgeons in Ireland in 1902. He was appointed resident medical officer and afterwards visiting medical officer to the fever hospital of the Belfast Union. When the Belfast Fever Hospital at Purdysburn was begun in 1903 he became its medical superintendent, and under his care

it rapidly became a model of what a modern hospital for infectious diseases should be.

It was in 1907 that Gardner Robb achieved distinction. A severe epidemic of cerebrospinal fever occurred in Belfast, and the death-rate of the first 230 cases was 70·4 per cent. When Robb used Flexner and Jobling's serum intrathecally he reduced the mortality to 29·2 per cent. These cases included fulminant types and patients of all ages. For many years afterwards his death-rate in sporadic cases was consistently less than one in three, and it was only with the advent of the sulphanilamide group of drugs that these results were bettered. He also contributed papers to the medical journals on acute poliomyelitis, on the antitoxin treatment of scarlet fever and on intubation in laryngeal diphtheria. He was a past president of the Ulster Medical Society, and of the Northern Ireland branch of the British Medical Association.

A colleague writes: Gardner Robb was not only an expert in hospital organisation and administration and keenly interested in every scientific and bacteriological advance, he was essentially a clinician, shrewd, observant and gifted with "the experiencing mind." By a few simple pertinent questions he would elicit from any patient capable of coöperation the essential points in the history of his symptoms, and he would describe simply and clearly the features of the case to his students. I remember him watching the choreiform movements of a patient suffering from acute encephalitis lethargica in the epidemic of 1920, and how he said "she has the movements, but these movements haven't the *abandon* of true chorea—the French word describes it best." Few men have achieved unsought so high a place in the esteem of the public and the affection of their colleagues. With no apparent effort he gained the confidence and trust of all who came in contact with him from city fathers to sick children. Generations of students remember his youthful figure as he moved from bed to bed eager to tell them all he knew. He spoke in low tones, because as he said "students listen more attentively if you speak quietly." It is sad to think that his voice is still.

LETTERS TO THE EDITOR

"FUNCTIONAL" NERVOUS DISEASE IN HOSPITAL PRACTICE

SIR,—Figures given of the incidence of psychoneurotic or "functional" disease in general and hospital practice vary widely. The following are drawn from my weekly outpatient department at the Seamen's Hospital, Greenwich, where casualty officers, outside doctors and colleagues within the hospital supplied the material, which was then shared with another physician on a calendar basis. Some selection of cases was made to suit particular interests, and this may have raised the proportion of psychoneurotics in my group to some degree. Otherwise, and essentially, this group represents about half the new medical outpatients attending the hospital in the selected year, 1938. They were men, women and children drawn from the neighbouring waterside district. Only about a quarter of them were or had been seamen.

Of 257 cases seen by me I have picked out 92 as psychoneurotic, because, after examination to the point of diagnosis (which was not necessarily made at the first interview) the psychogenic aspect was regarded as taking priority over the organic, in the sense that the *major* contribution to the patient's illness appeared to me to be an emotional derangement. In many of the cases the emotional factor was also the one with a prior demand for treatment.

INCIDENCE OF CASES OF "FUNCTIONAL" PRIORITY IN PATHOGENY

	New outpatients.	Functional cases.	Percentage.
Men	123 (Seamen 67)	36 (Seamen 19)	29 (Seamen 28)
Women	107	45	42
Children	27	11	41
Total	257	92	36

Some classification of these 92 cases—a third of the total—seemed necessary. The label "neurosis" is merely the start towards diagnosis, though through lack of skill, of time or of expert assistance this title remained on a number of case-sheets at the end of the year. A simple psychological history, often best taken at the second interview, usually permitted classification in one of the following five groups.

1. *With overt anxiety* (41 cases); (*a*) general 13, (*b*) with "conversion" symptoms 22, (*c*) with underlying obsessional or phobic traits 6. The presence or absence of overt anxiety makes a good starting-point in a simple classification. An "anxiety state" usually has localised somatic manifestations, for which some emotional explanation, however tentative, can be found in the history of the case. This somatic feature—e.g., dyspepsia—preceded by the term "anxiety" gives a useful way of subdividing this big group of cases.

2. *Conversion symptoms without overt anxiety* (21 cases).—These were recorded with the prefix letter "N," to indicate their nervous origin. They included dyspepsia, aerophagy, vomiting, dyspnœa, asthma, dermatitis, paroxysmal tachycardia, tics, enuresis, blindness and headache.

3. *True obsessional neurosis* (2 cases); 1 of which was treated by lengthy analysis.

4. *Traumatic and compensation neuroses* (8 cases).

5. *Neuroses incidental to other conditions* which had prior claims on treatment (12 cases).

6. *Unclassified* (8 cases).

The treatment of the cases offered considerable difficulty. Fortunately I was able to refer some to a skilled psychotherapist, who treated most of these by "short" methods, some improved by recognising and accepting the truth of the diagnosis, and for a few beneficial environmental changes were made. In nearly all the waste and expense of treating imaginary "organic" diseases were avoided.

I am, Sir, yours faithfully,

Castlebellingham, Dundalk, Ireland. RANYARD WEST.

A MONGREL

SIR,—Adhesiotomy! May I request the immediate and permanent suppression of this vile neologism which appeared in a leading article of your issue of May 11? This barbarism is not only redundant and mongrelly, it also fails to express the intended meaning: the suffix -otomy means cutting open, as in colotomy, gastrotomy, and many other words. Modern medical literature contains the following correct and widely-used synonyms: internal pneumonolysis, which, like pneumonokoniosis, can with advantage lose a syllable and become pneumolysis; adhesion cutting; and section or division of adhesions. Surely no more are needed?

To those who would neologise may I quote Fowler, in The King's English: "'It needs be that offences come; but woe to that man by whom the offence

cometh.' . . . It is well that each new word that does appear should be severely scrutinised."

I am, Sir, yours faithfully,

London. MAXWELL TELLING.

SULPHAPYRIDINE IN PNEUMONIA COMPLICATING PREGNANCY

SIR,—Reports of the use of sulphapyridine in pneumonia complicating advanced pregnancy are rare, so this case may be worth recording.

A woman of 25 was referred to me by Dr. Adelaide Roberts of Twickenham. She was then about 34 weeks pregnant. On Jan. 8 she was seized with a pain in the right side of the chest and when I saw her on the 10th she showed all the classical signs of a right-sided lower-lobe pneumonia, with temperature 101° F.; pulse 144, regular; respirations 50–60. The pelvis and pregnancy appeared normal and there was a trace of albumin in the urine, possibly due to the pneumonia. I had not had previous experience of the effect of M. & B. 693 at so advanced a stage of pregnancy. She was given 1 g. 4-hourly by day and night on the 10th and 11th. On the 12th her temperature had dropped to 98° F., pulse 100–120, respirations 20–30. The M. & B. 693 was continued in the same dosage until the 13th when the temperature, pulse and respiration were normal. Bronchial breathing was still present. The dosage was then dropped to 2 tablets t.d.s. She vomited once, but was relieved by sodium bicarbonate. On the 14th temperature, pulse and respirations were still normal so the dose was reduced to ½ g. t.d.s. She vomited once. The M. & B. 693 was discontinued on the 15th and the patient stayed in for a further fortnight and made an uninterrupted recovery. A fortnight after leaving hospital Dr. Roberts told me she was delivered of a normal well-developed live baby. The confinement was normal.

The anxiety of this case (a primipara) was the possibility of miscarriage or a dead baby, but nothing abnormal occurred. Advanced pregnancy seems therefore to be no contra-indication to the use of M. & B. 693 in the large doses required.

I am, Sir, yours faithfully,

Harley Street, W.1. GERALD SLOT.

SUGAR IN THE TREATMENT OF ULCERS

SIR,—I read with interest your Budapest correspondent's account in THE LANCET of May 4 (p. 826) of Dr. Szemkeö's treatment of ulcers with sugar. Thirty-five years ago I was an assistant to Dr. Engel-Reimers at St. George's Hospital, Hamburg, and he regularly used sugar with the addition of 1 per cent. naphthalin for the cure of varicose and other obstinate ulcers with great success. Since then I too have used the treatment widely in my practice at Hamburg with the same results.—I am, Sir, yours faithfully,

Swansea. ERNST A. MEYER.

STREPTOTHRIX EMPYEMA

STREPTOTHRIX infections are occasionally met with in the pleural cavity, the responsible organism being a mycelium which shows true branching and grows only on anaerobic culture. Dr. J. C. Gaffney showed films of pleural pus from two such cases to the section of pathology of the Royal Academy of Medicine in Ireland on April 19.

The first was a garage worker of 42, who was admitted to the Adelaide Hospital, Dublin, under Dr. Geoffrey Bewley in February, 1939, complaining of cough and weakness in the legs. About seven weeks before he had had "influenza," after which he had gone back to work but had not felt really well. His tongue was coated and his teeth were bad, his temperature was 100·2° F. and his pulse-rate 100, and there were signs of fluid over the left base. A paracentesis was performed and some thick foul-smelling pus was removed. Microscopic examination showed the presence of a streptothrix in large numbers, and the cells were all polymorphs. The pus was sterile on aerobic culture, but the organism was recovered after a few days anaerobic incubation. It was also found in the sputum. Closed intercostal drainage was performed, the cavity being washed out daily for about a week. The tube was removed at the end of a fortnight and the patient made an uneventful recovery. The second patient was a man of 81, who when seen on Dec. 8, 1939, by Dr. Buchanan had acute abdominal pain with general tenderness and rigidity. His temperature was 103° F. and pulse-rate 120, and there was dullness over the base of the right lung. A diagnosis of pneumonia was made and the presence of fluid was suspected. He was given M. & B. 693. Aspiration produced some opalescent fluid in which all the cells were polymorphs and an occasional diplococcus was seen. It was sterile on culture. The patient improved until Jan. 17, 1940, when his temperature rose to 100° F., and his pulse-rate to 100. On Jan. 23 the chest was explored, and some thick foul-smelling pus was removed. It showed a streptothrix in large numbers which subsequently was grown in anaerobic culture. On Jan. 26 tube drainage was performed, and though his convalescence has been slow his general condition is now good. Dr. J. J. McCann described a case of streptothrix pneumonia in a thin tuberculous-looking child who looked extremely ill and had exceptionally heavy sweats with an intermittent temperature. There were râles and rhonchi all over the chest and signs of bronchopneumonia on the left side. When the sputum was examined there was no thought of streptothrix infection.

Dr. R. A. Q. O'Meara, the president, said that these cases emphasised the importance of examining sputum and determining exactly the type of organism present in empyema fluid. In Dr. Gaffney's cases he thought that the organism was a streptothrix closely related to actinomyces, and in Dr. McCann's he thought the organism was *Streptobacillus moniliformis*. All these organisms appear to respond reasonably well to treatment with iodides. Dr. W. Hayes suggested that streptothrix empyemas nearly always start as a primary condition of the lung, and that a small lung abscess develops and becomes shut off, oxygen being absorbed from the abscess cavity. Such a process would create conditions suitable for the growth of streptothrices, which may often be found in the mouths of normal people. The abscess may then rupture into the pleural cavity. Dr. W. A. Gillespie said that in rats the *Streptobacillus moniliformis* is found in partnership with one of the pleuropneumonic organisms. He asked if any of these were known to be pathogenic for man, to which the President answered no. Dr. A. R. Parsons referred to a patient who had loss of voice and a bad cough. A laryngologist thought that he was suffering from syphilis of the larynx, but the Wassermann test was negative. The radiogram did not look at all like tuberculosis and the radiologist thought that it resembled what he had seen in streptothrix infection of the lungs. On examination of the sputum a streptothrix was isolated, and tubercle bacilli were also found.

Dr. Gaffney, in replying to questions, said that this condition must be more common than is generally recognised. He did not think that the rate of streptothrix infections would be much increased because of rat-infested houses; such houses had been in existence for a long time. The actual source of infection by the streptothrix is still unknown. The sputum in these cases, he said, is always very fœtid, and an ordinary gram stain will nearly always indicate the presence of a streptothrix.

WITH THE B.E.F.

MEDICUS, M.P., IN FRANCE

I WAS at General Headquarters of the B.E.F. on Thursday evening, May 9, and was wakened by the air-raid syren shrieking its warning at about 4.30 A.M. on the morning of May 10. The vast offensive of the Germans had begun. Holland, Belgium and Luxembourg were invaded, bombs were exploding with dull crumps near by. Anti-aircraft guns and machine-guns roared, the drone of bombing planes and the high-pitched note of the fighter engines weaved an infernal tapestry of sound in the air.

When the news from other places came in, it appeared that the Germans had carefully synchronised their attack to begin at many points on the frontiers, by land armies and in the air, over a very wide area. Passing through towns and villages on my way back to England I heard the same story. At the French ports it was the same again—the air-raid warning and the attack from the air. And when I had to wait a day at a French port to get a boat to bring me home, there was, it seemed, a constant succession of air-raid warnings—so frequent, in fact, as to lose their effect. French civilians and soldiers seemed to pay very little attention to them.

But what a difference between France and England. In the fields of France the ground, wonderfully cultivated, being tended by old men and women, children and obviously invalid or unfit men. In the towns and villages very few men of even apparent military age not already in uniform, and women actively engaged in every kind of occupation. Another contrast was that between the "other war" of 1914–18 and this war. Then we, the British soldiers of that day were the politely received and kindly treated guests of the French nation. Our zones were separated from theirs, our liaison with them friendly but not affecting us in our own areas very much. Now the British are almost part of the French nation; we are mixed up with them as their own soldiers are, and our official liaison with them is a matter affecting all of us every day and all the time. The British soldier now is more than a friend courteously received, he is a member of the family.

* * *

Before the German offensive began I had spent five days in France and had seen a great deal of the medical organisation of the armies from the base to the front-line positions. I was privileged to discuss the general plan of the organisation at the Medical G.H.Q. and then to see regimental, divisional, corps and army arrangements. I drove very many miles, I tramped over long distances of the front line along the Belgian frontier, I visited hospitals, field ambulances, mobile bath units, refrigerator units for blood-transfusion, motor ambulance units and many other of the complex adjuncts of the modern medical and sanitary armoury.

The medical organisation of the armies is admirable, its personnel well trained, its equipment very comprehensive, its medical officers and other ranks in very good heart and its only complaint, before the German offensive, was of lack of active work. Now when it is being tested like the rest of the armies as no organisation has ever been tested before it is doing splendid work. And perhaps I may reveal now some things which when I took the notes—some only in my mind as I did not wish to put words on paper—I did not think I should be able to do. The kind of attack to be made by the Germans, with tanks breaking through the lines and surging around fortified positions like the tide around rocks on the shore, was foreseen and planned for. The low-flying dive bomber supporting the tank and machine-gunning was foreseen and planned against. Details I cannot give, but the difference this type of warfare makes is partly the enormous lengthening of medical lines of communication. Where in the last war the distance between the front line, the advanced dressing station, the main dressing station and the casualty clearing station were measured in yards and furlongs, now they are measured in miles. This difference of distances means many changes in the organisation of the medical and other services. It also makes the front less stable. A greater fluctuation of the line of the fighting front will probably be normal. But above all it makes one serious difference to the medical profession. It demands more doctors and again more doctors for the medical service of clearing the wounded from the front line to the C.C.S. In this war too there are more numerous special units of one kind or another. Many more aerodromes, for instance, with large non-Air Force personnel. More engineering and transport units. More artillery units. And more other units from lumbermen and railwaymen to units of Czechs and Poles. Any of these units may need and claim the services of a medical officer. The demand for volunteer doctors up to the age of 55 may fill the gap for a time, but is likely to be followed by more demands still.

The provision of medical services for the Army, the Navy and the Air Force will almost certainly mean rationing of medical services for the civilian population. In a war which includes the civilian population and our own country as well as the armies overseas on a foreign soil the distinction between civilian and Army medical work is more one of degree than of kind. It may therefore be necessary to look at the problem of provision for the civil population and the armed forces as that of one medical service divided up into civilian (including the vital A.R.P. work), Army, Navy and Air Force as sections of the service.

* * *

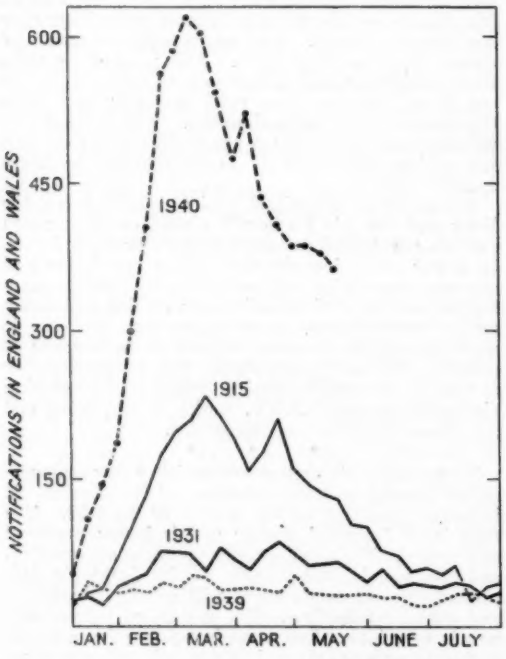
To conclude this preliminary article a few sentences on the general physical condition of the Armies. It is better than that of the armies of 1914–18. The food is of improved quality and is better prepared and cooked. The arrangements for baths are excellent and the mobile bath should be invaluable in this present type of warfare and will greatly lessen skin and parasite infections. The morale of officers and men is very high. The army is fighting for a cause, a cause it understands and in which it believes. And it is a better informed army than that of 1914–18.

THE report for 1939 of the home service ambulance committee of the Order of St. John and the British Red Cross Society is a fine record. During the year the service's ambulances have carried over 220,000 patients, and since the beginning of the war additional convoy work has been undertaken for the R.A.F., while the various coastal ambulance stations have answered many calls from shipwrecks. The committee say that the need today is for four-stretcher ambulances and they do not consider that the chassis of a private motor-car is suitable for conversion into an ambulance. The ambulances from headquarters in London were much in demand during the early days of evacuation, for they are not restricted by boundaries, and during 1939 they carried 5149 patients, which was well over a thousand more than during the previous year. Most of this increase was due to patients carried in connexion with the Emergency Bed Service. The war has postponed the establishment of a 24-hour service in association with this organisation.

PUBLIC HEALTH

Cerebrospinal Fever

IN the first nineteen weeks of this year the notifications of cerebrospinal fever (including non-civilian cases) have reached the unprecedented total of 7398, more than twice as many as in the whole of 1915 and at least five to six times as many as in a normal non-epidemic year. The maximum point of the present epidemic was reached, after a series of rapid weekly rises, at the end of February or beginning of March. An equally rapid decline was not to be hoped for, as was pointed out at the time (LANCET, March 23, p. 567), and is in fact not being realised. The graph shows the relatively slow fall that has been taking place, comparable with the experience of 1915, though the fine weather of the



past three weeks has accelerated the fall. This time last year notifications numbered some 30–35 weekly, in the epidemic of 1931 they were 60–70, at the beginning of the present month the figure was still unfortunately only a little below 400. Recently the counties of Lancashire and Glamorgan have been relatively heavy contributors.

Complete mortality figures are not yet available but on page 966 of this issue Dr. Stanley Banks quotes some provisional figures supplied by the Ministry of Health. For the first quarter of the year they report 1100 deaths and a crude fatality-rate of 22 per cent. (civilian and non-civilian cases combined). Almost the same figure (24 per cent.) is given by Underwood as a result of special inquiry in a few large areas (*Brit. med. J.* May 11, p. 757). This is clearly a great improvement on the rate of 60 per cent. or thereabouts that has usually prevailed in the past but is not as good as the more restricted experiences that have been reported may have led some to hope for. Much local variation in the fatality-rate is, however, apparent. In Cardiff—Dr. Emrys Harries describes the treatment given there on p. 967—it has been particularly low, 11 per cent. only. In Leeds and the West Riding it has, according to Underwood, been 30–35 per cent. There are at present too many unknown factors in these differences to be resolved—e.g., the prevailing age of attack. According to the Ministry's provisional figures the fatality-rate is about 50 per cent. in infancy and at ages over 45.

Infectious Disease in England and Wales

DURING THE WEEK ENDED MAY 4, 1940

Notifications.—The following cases of infectious disease were notified during the week: smallpox, 0; scarlet fever, 946; whooping-cough, 630; diphtheria, 701; enteric fever, 33; measles (excluding rubella), 5286; pneumonia (primary or influenzal), 883; puerperal pyrexia, 156; cerebrospinal fever, 377; poliomyelitis, 2; polio-encephalitis, 2; encephalitis lethargica, 4; dysentery, 80; ophthalmia neonatorum 109. No case of cholera, plague or typhus fever was notified during the week.

The number of civilian and service sick in the Infectious Hospitals of the London County Council on May 3 was 917 made up of: scarlet fever, 139; diphtheria, 120; measles, 15; whooping-cough, 43; enteritis, 68; chicken-pox, 59; erysipelas, 39; mumps, 14; poliomyelitis, 1; dysentery, 7; cerebrospinal fever, 94; puerperal sepsis, 23; enteric fevers, 11; german measles, 94; meningitis, 1; other diseases (non-infectious), 79; not yet diagnosed, 110.

Deaths.—In 126 great towns, including London, there was no death from smallpox or from enteric fever, 1 (0) from scarlet fever, 7 (0) from measles, 1 (0) from whooping-cough, 15 (1) from diphtheria, 26 (5) from diarrhœa and enteritis under 2 years, and 35 (4) from influenza. The figures in parentheses are those for London itself.

Stockport reported 3 deaths from diphtheria, and there were 9 fatal cases of diarrhœa in Birmingham.

HOSPITAL OF ST. JOHN OF JERUSALEM

THE last report of the ophthalmic hospital maintained in Jerusalem by the Order of St. John reflected the disturbed condition of Palestine; the latest report, for 1939, shows the improved conditions in the country. The total attendances for 1938 were 79,018; in 1939 they were 97,403. The contrast is still more striking if one compares the attendances since the beginning of the war, which has had the effect of bringing the factions of Jew and Arab together and uniting them against a common danger. The importance of ophthalmic work in a country where eye diseases are so rife can hardly be appreciated here, for Sir John Strathearn, M.D., the warden, states that of the new patients seen 90·33 per cent. had trachoma; and the high quality of the work done may be gauged from the fact that during the year 251 cataracts were operated upon. Some idea of the conditions under which the work is carried out may be gathered from a letter from the warden who says "The few fellahin who come (and particularly the children) are literally starving when admitted to hospital and one dare not operate on many until they are better nourished."

For many years the work of the hospital has been restricted for want of better accommodation for patients and improved facilities for the treatment which modern advances demand. In spite of the unsettled times the chapter-general of the order has sanctioned the addition of a new wing which will supply these facilities. Provision has also been made for physiotherapy, and for paying patients. The plans for part of this wing, which will cost some £15,000, have been approved and building is proceeding.

PARLIAMENT

ON THE FLOOR OF THE HOUSE

By MEDICUS, M.P.

THE House of Commons is really a very remarkable institution. On Tuesday evening of this week, with preparations for the organisation of Local Defence Volunteers going on all over the country and with grave news of the fighting in France, our procedure went on much as usual. We had questions and it appeared that the Local Defence Volunteer organisation was to be dealt with in a bill to be passed through all its stages on Wednesday. Treachery is also to be the subject of a bill and it is reassuring to know that the House keeps its balance so well that any clauses which infringe liberty, as apart from reasonable criticism, will be severely handled. At question time a private notice question raised the important matter of how the business of the House is to be conducted when there is no opposition party capable, in an emergency, of forming an alternative government. Sir Stafford Cripps spoke on this and so did Dr. Haden Guest, who raised the point that the selection of the debate on supply, which determines which votes shall be criticised, was not a difficulty as all parties supported the Government.

* * *

The arrangement about the Opposition choosing supply days came into existence in 1896 when the number of supply days was reduced to twenty and the opportunity of criticism was correspondingly reduced. It was then felt that in order to have a fair arrangement the Opposition should choose its field of criticism—that is, when the supply vote should be debated—and the Government would then arrange this. This is not a rule of the House but a custom or convention. How is the arrangement to work now? No-one quite knows, and the Speaker wisely left the question open and suggested that the House should be given time to "shake down."

* * *

Equally difficult questions exist for the party organisations and some serious and intricate problems are being faced by both Conservatives and Labour. Probably all will "shake down," to use the Speaker's words. But members realise that what is involved is not a detail of procedure but the question of the safeguarding of the constitutional right of full and free criticism. After such a recent demonstration of the power of an Opposition in the re-forming of the Government under Mr. Churchill the value of Opposition criticism could hardly be challenged.

After that the House settled down to a debate on the Colonial Development and Welfare Bill and debated until 9.30 P.M. A useful and constructive debate showing that the House is the guardian of the Colonial peoples and is planning to help them even in this grave hour.

MEDICAL NEWS

University of Cambridge

The following examiners for the diploma in medical radiology and electrology in 1941 have been appointed:

Part I: Prof. G. Stead, Prof. Sydney Russ, D.Sc.; *Part II:* Dr. A. E. Barclay, Dr. Philippe Bauwens, and Dr. Russell Reynolds.

Royal College of Surgeons of Edinburgh

At a meeting of the college held recently, with Dr. H. M. Traquair, the president, in the chair, the following were admitted to the fellowship:

J. C. Andreas, M.D. Manitoba; Harigopal Barat, M.B. Calcutta; L. L. Bernstein, L.R.C.P.E.; B. B. Bhatia, M.B. Lucknow; W. A. Coe, M.B. Edin.; R. J. Crompton, M.B. Durh.; B. J. D. Dunne, M.B. N.Z.; K. J. Eager, M.B. Melb.; J. R. Frank, M.B. Edin.; D. F. Freebody, M.B. Lond.; J. G. O. Hamman, M.B. Cape Town; B. A. Jackson, M.D. Toronto; J. O. Kelly, M.B. Edin.; A. B. Morrison, L.R.C.P.E.; K. S. Mullard, M.B. Camb.; G. D. Oliver, M.D. Manitoba; G. I. M. Ross, M.B. Edin.; L. M. Rouillard, M.R.C.S.; Gurbachan Singh-Janda, M.R.C.S.; Ebenezer Thomas, M.B. Madras; L. R. Williams, M.D. McGill; R. W. Wyse, M.B. Glasg.; and J. D. Younghusband, M.B. Camb.

West Kent Medico-Chirurgical Society

The annual dinner of this society will be held on Thursday, June 13, at Chiesman's Restaurant, Lewisham High Street, S.E.13. Further particulars may be had from the hon. secretary, Dr. C. J. B. Buchan, 267, Baring Road, Grove Park, S.E.12.

Second Addendum to B.P.

The General Medical Council will publish shortly a second addendum to the British Pharmacopœia, 1932, in which new monographs, and modifications of existing monographs, will be included. When a new addendum has been ready for publication, it has been customary to give facilities for advance copies to be inspected, during the three months before publication, by medical practitioners, pharmacists, analysts, manufacturers, and others who may be interested. But this addendum has been prepared to deal with conditions arising from the present emergency, and it is expedient that it should be published, and thus made official, without delay. It is not possible, therefore, to provide for the customary preliminary inspection of the completed addendum, but arrangements have been made for a limited number of advance proofs to be available, on application, to manufacturers of the new preparations described in this addendum. The following new monographs will be included:

Emulsio olei morrhuæ
Emulsio olei vitaminati
Extractum malti cum oleo vitaminato
Liquor vitamini A concentratus
Liquor vitamini D concentratus
Liquor vitaminorum A et D concentratus
Oleum amygdalæ volatile purificatum
Oleum hippoglossi
Oleum vitaminatum
Toxinum tetanicum detoxicatum

Manufacturers interested in the production of these articles should apply to the secretary of the British Pharmacopœia Commission, 44, Hallam Street, London, W.1, for advance copies of the monographs.

The addendum will also contain emendations to monographs of the British Pharmacopœia, 1932, authorising the use of arachis oil, cotton seed oil or sesame oil, in place of olive oil, in making liniment of camphor, hydrous ointment, and compound ointment of mercury; and the use of simple ointment in place of the prescribed fatty basis in making ointment of tannic acid and ointment of capsicum. As these alterations are permissive, not compulsory, the usual preliminary inspection of the formulæ is not deemed necessary. No additional monograph, or emendation of a monograph, is official until the second addendum has been published.

Royal Free Hospital

The following scholarships are open to former students of the hospital:

A. M. Bird scholarship—£200 for one year tenable from Aug. 1, to enable a medical graduate to obtain general experience in pathology.

Mabel Webb and A. M. Bird research scholarship—£200 a year for assistance in carrying on research.

Further particulars and form of application can be obtained from the secretary of the medical school, Hunter Street, London, W.C.1. Applications must be received by June 10.

Ministry of Health

The Minister of Health, Mr. Malcolm MacDonald, has appointed Sir Edmund Brocklebank to be his parliamentary private secretary, Mr. S. F. Wilkinson to be his private secretary, and Mr. R. F. Tyas to be his assistant private secretary.

Committee on Recruiting Problems

The Minister of Labour has appointed a committee to advise him on medical problems arising in connexion with the examination of men by civilian medical boards. The committee will take evidence from experts on eyesight and hearing, orthopædics and other matters brought to the notice of the boards. The following have been appointed: Lord Horder (chairman), Surgeon Captain C. H. M. Gimlette (Admiralty), Dr. W. Haward (Ministry of Pensions), Dr. T. D. Kennedy (Department of Health for Scotland), Colonel J. A. Manifold (War Office), Dr. Geoffrey Marshall (Royal College of Physicians), Group-Captain d'Arcy Power (Air Ministry), Dr. N. F. Smith (Ministry of Health), Mr. G. C. Veysey (Ministry of Labour), Dr. R. E. Whitting (Ministry of Health). Dr. A. E. Hallinan and Mr. E. W. Hoyle (joint secretaries).

Irish Hospital Bed Bureau

Our Irish Correspondent writes: The bill to provide for the establishment of a hospital bed bureau has now passed both legislative chambers. Much alarm was created by the terms of the bill as introduced, for it appeared to place so much power in the hands of the minister that little of the independence of the voluntary hospitals would remain. Fortunately, subsequent to the publication of the bill, the minister recognised that public opinion was adverse to many of its provisions, and he consented to make or to accept radical amendments which remove the most objectionable provisions. There is still grave doubt as to the utility of the measure until there has been a considerable increase in the number of beds available in the voluntary hospitals. The bureau is intended to facilitate the admission of patients to hospital, but if no beds are available it will have nothing to work on.

In many particulars, however, the act will differ in essentials from the bill as introduced. The provision that the bill would apply to all hospitals which had ever received help from sweepstake proceeds has disappeared, and instead the measure will only apply to hospitals which receive such help after the date of the passing of the act. In its original form the committee in charge of the bureau was to have been appointed by the minister and its members subject to removal by him at any time, whereas it is now provided that the members of the committee will in fact be nominated by the individual hospitals. The scope of the regulations to be made for the working of the bureau has been carefully limited so as to prevent its interfering with the independence of the hospitals. In several other instances the Minister for Local Government and Public Health, who was in charge of the bill, expressed his willingness to meet the suggestions of his critics in his regulations, while considering it unnecessary that they should appear in the statute. Those who are interested in the voluntary hospitals, while not altogether satisfied with the bill, recognise that the minister took trouble to understand their views, and came a good distance to meet their case.

Cardiac Society of Great Britain and Ireland

The annual meeting of this society was held in the cardiac department of the London Hospital on May 9, under the chairmanship of Dr. John Parkinson. After a debate on fitness for war service, a committee was appointed to investigate and make recommendations on the cardiac examination of recruits. In the afternoon there was a demonstration of cases, radiograms and electrocardiograms. This was followed by a discussion on the effort syndrome, with special reference to military service. Original communications included papers on auricular septal defect, special forms of infective endocarditis and surgical aspects of hypertension with unilateral renal damage.

Medical Diary

Week beginning May 27

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1.
MONDAY
Odontology.—at 5 P.M., annual general meeting. Sir Frank Colyer: Dental Variations in Preuss's Colobus.
FRIDAY
Radiology.—6 P.M., (32, Welbeck Street, W.1), annual general meeting.

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1.
THURSDAY.—2.30 P.M., Mr. John Read, Ph.D., Dr. F. G. Spear, Dr. J. C. Mottram, and Mr. L. H. Gray, Ph.D.: Physical and Biological Experiments with Neutrons. 6.30 P.M., annual general meeting.

FACULTY OF RADIOLOGISTS, 32, Welbeck Street, W.1.
FRIDAY.—11 A.M., Dr. S. Cochrane Shanks: presidential address. 2.30 P.M., Dr. S. Whately Davidson and Lieutenant J. Dudfield Rose: Gastroscopy and Gastric Radiology. Mr. Hermon Taylor, Dr. G. R. Mather Cordiner, and Dr. J. C. Hawksley will also speak.
SATURDAY.—10.30 A.M., Prof. G. Hadfield, Mr. L. E. C. Norbury, Dr. F. Ellis, Dr. R. W. Scarff, Mr. T. A. Green, Dr. J. R. Nuttall: The Value, Technique, and Limitations of Biopsy.

ROYAL INSTITUTION, 21, Albemarle Street, W.1.
TUESDAY.—5.15 P.M., Prof. V. H. Mottram: Food and the Housewife.
FRIDAY.—9 P.M., Prof. W. W. C. Topley, F.R.S.: Bacteria in the Air.

WEST KENT MEDICO-CHIRURGICAL SOCIETY.
THURSDAY.—4 P.M. (Miller General Hospital, S.E.10), Sir Walter Langdon-Brown: Salt and Water. (Purvis oration.)

BRITISH POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12.
MONDAY.—10 A.M., opening of special course on war medicine.
TUESDAY.—2.30 P.M., Sir Walter Langdon-Brown: ward clinic.
WEDNESDAY.—11.30 A.M., clinico-pathological conference (medical). 2 P.M., Dr. T. C. Stamp: The Bacteriology and Diagnosis of Venereal Diseases (Gonorrhœa). 3 P.M., clinico-pathological conference (surgical). 4.30 P.M., Prof. G. R. Cameron, D.Sc.: Pathology of the Liver.
THURSDAY.—2 P.M., Dr. Duncan White: radiological conference.
FRIDAY.—2 P.M., clinico-pathological conference (gynæcological). 2.30 P.M., Mr. V. B. Green-Armytage: sterility clinic.
DAILY.—10 A.M.–4 P.M., medical clinics; surgical clinics and operations; obstetrical and gynæcological clinics and operations. 1.30–2 P.M., post-mortem demonstration.

FELLOWSHIP OF MEDICINE AND POSTGRADUATE MEDICAL ASSOCIATION, 1, Wimpole Street, W.1.
WEDNESDAY and FRIDAY.—6 P.M. (London Chest Hospital, Victoria Park, E.2), M.R.C.P. course in heart and lung diseases.

Vacancies

Barbados General Hosp.—H.S., £325.
*Battersea General Hosp., S.W.*11.—H.P., at rate of £100.
Bradford City Sanatorium, Grassington.—Asst. M.O., £175.
Belfast, Forster Green Hosp., Forthbreda.—H.P., at rate of £150.
Bury St. Edmunds, West Suffolk General Hosp.—H.S., £150.
Cambridge, Addenbrooke's Hosp.—H.P., at rate of £130.
Cardiff, King Edward VII Welsh National Memorial Assn.—Area asst. tuber. O., at rate of £500.
Chester Royal Infirmary.—H.P. and 2 H.S.'s each £150.
Coventry and Warwickshire Hosp.—Two H.S.'s to spec. depts., each at rate of £150.
Exeter, Royal Devon and Exeter Hosp.—H.S., at rate of £160.
Gloucestershire County Council.—Asst. county M.O.H., £600.
Grimsby and District Hosp.—H.P., at rate of £175.
Hertfordshire County Council.—Asst. school M.O.'s, each £500.
Hull Corporation.—A.M.O. at Beverley Road Hosp., £350. Also Temp. asst. M.O.H., £600.
Indian Medical Service.—Emergency Commissions.
London County Council.—Temp. asst. M.O. (Class I) for King George V Sanatorium, Godalming, £350.
Manchester, Ancoats Hosp.—Res. M.O., at rate of £150.
Middlesbrough, North Riding Infirmary.—Cas. O. & H.P., at rate of £150 and £140 respectively.
Newcastle upon Tyne City and County.—Res. surg. O. for Newcastle General Hosp., £550.
Northallerton Emergency Hosp.—Med. supt., £900.
Northumberland County Council, Wooley Sanatorium.—Med. supt., £650.
Princess Beatrice Hosp., Earl's Court, S.W.5.—Res. H.S. and cas. O. and res. H.P. and cas. O., each at rate of £110.
Rochdale Infirmary and Dispensary.—Second H.S., £150.
Romford, Oldchurch County Hosp.—Asst. res. surgeon, £350. Also jun. res. M.O., £250.
*Royal Cancer Hosp. (Free), Fulham Road, S.W.*3.—Second asst. pathologist, £300.
*St. Mark's Hosp. for Cancer, City Road, E.C.*1.—H.S., £120.
*Samaritan Free Hosp. for Women, Marylebone Road, N.W.*1.—H.S., at rate of £100.
Wakefield, Clayton Hosp.—H.S., at rate of £150.

The Chief Inspector of Factories announces a vacancy for an examining surgeon at Kirkmichael, Dumfries.

NOTES, COMMENTS AND ABSTRACTS

ANALYSIS UNDER HYPNOTICS

IN the first of two papers read at the meeting of the Medical Society of Individual Psychology on May 9 Dr. Henry V. Dicks said that many patients after anæsthesia with Evipan and Pentothal display a suggestible euphoric state which is very suitable for psychological investigations. He described Campbell's technique which he uses and the precautions he adopts, which render the use of either evipan or pentothal safe even with outpatients. He has found no material difference in the effects of the two drugs. The method sometimes yields surprisingly rapid insight into "depth mechanisms" which are entirely forgotten by the patients in their normal state. He quoted as examples a case of paranoid jealousy in a married woman, where the essential projection mechanism and other important factors came to light in one session, and a case of claustrophobia in a young married woman where a complicated identification and displacement were discovered, the nature of which had been unsuspected. Other cases have been less successful, while in some the investigation has been without result owing to absence of the desired euphoria or to resistance factors the nature and incidence of which is unknown. In treatment evipan is most useful in cases of hysterical conversion and amnesia, when it serves as a reliable substitute for hypnosis. This may prove a valuable way of obtaining quick relief in many hysterical war neuroses where time has to be saved. Where evipan has been used to overcome resistance during the progress of an analysis, or with the object of promoting emotional abreaction, it has not been uniformly successful, for not all patients display the necessary "post-anæsthetic" state. In a case of alcoholism evipan has proved of value both as a substitute and as a means of facilitating the recital of distasteful early memories. Dr. Dicks also quoted an experiment designed to test the power of evipan to cause a person to divulge information he wished to withhold, such as might be practised on criminals or prisoners. This experiment failed, for the subject had complete control over his words on waking. In conclusion, Dr. Dicks said that evipan and allied substances are a useful weapon in diagnosis and in psychopathological research. In treatment they can take the place of hypnosis in the rapid cure of hysterical phenomena, but are no substitute for the real work of analysis of underlying conflicts. The factors making for success or failure cannot yet be defined; the existence of good rapport or a positive transference seem important, and the element of surprise is also useful. Patients are evidently able to form resistances to repeated injections. There is also a pharmacological limitation to frequent administration of what are, after all, toxic substances.

In the second paper Dr. Ellis Stungo said analysis is a superficial investigation into the psyche, and the use of drugs in that connexion implies an even more superficial type of inquiry with the object of achieving rapid results. This is not necessarily the case, for it is possible to gain a profound knowledge of the patient's personality, character, motives, goals and conflicts by means of evipan analysis. His technique consists of injecting evipan sodium intravenously in sub-anæsthetic doses, so producing a light narcosis or hypnotic state. Evipan acts on the higher cortical centres and its effect is to inhibit inhibition. The patient's resistance, conscious or unconscious, is thus overcome, and the doctor can obtain intimate details of personal history which do not depend on the discretion, judgment or good taste of the patient. Information is neither suppressed nor distorted. Uncoöperative patients become accessible, and the development of transference is not as essential as with other psychological techniques. Dr. Stungo maintained that evipan analysis is a practical measure, which is what the patient wants. In his opinion too much time is taken up by psychotherapeutists in searching for life conflicts when all that is required is the eradication of symptoms produced by an acute conflict. This has been successfully achieved in several cases by one evipan investigation and there is no reason to fear relapse on account of rapidity of treatment or analytical superficiality. Cases of long-standing neurosis require deeper analysis, and this can sometimes be achieved by repeated evipan investigation. There are no contra-indications to such a procedure. The most practical application of evipan analysis at the present time is in the treatment of nervous war casualties. These will comprise traumatic cases, cases of anxiety, anxiety hysteria and hysterical conversion, neuroses associated with organic disorders and malingering. Such cases require prompt and effective treatment and evipan is particularly well suited for the purpose. Readily administered, rapidly effective, short-acting, safe in moderate doses, it presents a means of combining diagnosis and treatment. A small dose will immediately calm cases of simple panic. Agitated patients can be anæsthetised by larger quantities, the injured can be relieved of pain and the evipan used for anæsthetic purposes, and malingerers can be readily detected.

HUMAN VIRUS INFECTIONS OF ANIMAL ORIGIN

IN his Chadwick lecture at the London School of Hygiene and Tropical Medicine on May 21 Prof. S. P. Bedson discussed the mode of spread and control of human virus infections of animal origin. None of these, he said, constitutes a major public-health problem but the underlying principles concerned in their control are of general application. Viruses are spread directly in the same way as are micro-organisms, it is only when one comes to the indirect method of spread of infection by water, milk and food that a difference between bacteria and viruses is found, for virus diseases are rarely, if ever, spread by these means. The four virus diseases cowpox, rabies, equine encephalomyelitis and psittacosis represent three modes of transmission: by direct contact, by insects and by the inhalation of infective particles. The eradication of rabies from this country has been rendered possible by our geographical position and the thoroughness with which antirabic measures have been applied. The importance of psittacosis as a disease of man has been increased by the demonstration that birds of the parrot family are not alone susceptible even under natural conditions. Human beings have contracted the disease from fulmar petrels in the Faroes and in Iceland and the other seabirds may be susceptible. The partial failure of the embargo on the importing of parrots and parrakeets in the control of psittacosis in this country is attributed to infection of the home stocks and the occurrence of apparently healthy carrier birds; the existence of the latter largely nullifies quarantine measures applied to incoming birds though the application of the complement-fixation test in the detection of the infected birds might render quarantine effective.

NEW PREPARATIONS

"HYPOLOID" STIBOPHEN.—Under this name Burroughs Wellcome and Co. (Snow Hill Buildings, London, E.C.1) are now producing in this country a trivalent antimony compound of sodium pyrocatecholdisulphonate containing the equivalent of 1 per cent. of antimony trioxide in organic combination. Its manufacture is undertaken by licence under the English patent No. 376346, the objective substance of which is Fouadin (Stibophen). It is presented in an isotonic solution (6·3 per cent.) for intramuscular injection in the treatment of schistosomiasis and is issued in two different packings, one for adults and the other for children. Each package contains the

required number of Hypoloid ampoules in graduated doses for a single course of treatment.

BRITISH JOURNAL OF SURGERY

THE April issue (Vol. 27, No. 108) contains the following articles:

COLLES'S FRACTURE. By J. H. Mayer (London). The frequent failures in the treatment of Colles's fracture are attributed to slipping of the lower fragment in the splint after reduction. The essential part of the reduction is described as being a pronation-twist, and the author holds that to retain the correct position the elbow must be included in the plaster.

A FURTHER REVIEW OF THE INTERINNOMINO-ABDOMINAL OPERATION: ELEVEN PERSONAL CASES. By Gordon Gordon-Taylor (London). Six further operations are reported, making the author's total eleven. Seven of the eleven have survived operation. The technique is briefly discussed, and the importance of nerve-blocking and also of instituting drip infusion before operation are stressed.

A NEW CONCEPTION OF PARATHYROID FUNCTION AND ITS CLINICAL APPLICATION. By Arthur J. Helfet (London). The theory expounded is that parathormone controls the inorganic-phosphate level in the blood by stimulating excretion of phosphate by the kidney, and by mobilising calcium ions from the bones to combine with the phosphate and render it soluble and excretable as calcium phosphate. The phosphorus intake is lessened by administration of aluminium acetate, which combines with the phosphate. The application to diseases of bones is described.

ANNULAR PANCREAS. By G. J. Cunningham (Brighton). In the case described the condition was symptomless. The abnormal part of the pancreas originated from a ventral bud, and its duct had an independent entrance into the common bile-duct.

OSTEO-ARTHRITIS OF THE HIP. By L. W. Plewes (Oxford). In slightly more than half of the 242 cases analysed a definite cause was found and the majority of these were unilateral. Injury and slipped epiphysis were the commonest ætiological factors. Deep X-ray therapy gave encouraging results.

THE SURGICAL TREATMENT OF MID-ŒSOPHAGEAL CARCINOMA. By Harold Wookey (Toronto). The operation is performed in stages. First a gastrostomy is made; then the œsophagus is exposed in the neck and marked by a silver wire. Five days later the œsophagus is exposed by the intrathoracic route, approaching from the right side, aided by division of the vena azygos major. The œsophagus is divided below the growth and removed via the neck. Later the œsophagus is reconstructed by a skin tube. Two of four cases survived operation. One is still well.

BIRTH FRACTURE OF THE TIBIA. By Bryan McFarland. The extreme difficulties of obtaining union are described. The author has been successful in two cases by use of a "by-pass" graft.

SIALOANGIECTASIS. By George Swinburne (Melbourne). The condition is a dilatation of the ducts, terminal ductules and alveoli of the salivary glands. A well-marked case is described, secondary to chronic parotitis. The patient developed pernicious anæmia. The pathology is discussed.

POST-TRAUMATIC CEREBROSPINAL RHINORRHŒA WITH CASE REPORT. By William Gissane and B. K. Rank (London). The early and delayed forms of the complication are distinguished and the lethal nature of the latter commented on. Operative closure of the defect is advised. A successful operation, performed four months after the original injury, is described. A tibial graft was used to close a defect in the roof of the frontal sinus.

ON THE MUSCLE-FIBRES OF THE ANAL SUBMUCOSA, WITH SPECIAL REFERENCE TO THE PECTEN BAND. By J. Fine and C. H. Wickham Lawes (London). Histological examination of post-mortem and biopsy specimens have shown the presence of involuntary muscle-fibres in the submucosa, which form a dense band in cases with annular thickening of the anal submucosa. This thickening, it is concluded, is the "pecten band."

A CASE OF ADRENAL CORTICAL HYPERPLASIA, ASSOCIATED WITH PSEUDO-HERMAPHRODITISM. By I. Douglas Miller and P. J. Kenny. The child had been unsuspectingly brought up as a male till the age of ten years. He had a very marked cortical adrenal hyperplasia, and at operation a well-developed uterus, adnexa and a small vagina opening into the urethra, with a rudimentary penis and hypospadias.

THE TECHNIQUE OF BRACHIAL PLEXUS BLOCK ANÆSTHESIA. By J. Patrick (Sheffield). The supraclavicular route has been used successfully in a consecutive series of 44 cases, with only 1 failure and a complication in 11 other cases. The technique is described, with the dangers to be avoided.

CANCER OF THE STOMACH AS A SURGICAL PROBLEM. By Reginald T. Payne (London). An analysis is given of 506 cases admitted to the wards of St. Bartholomew's Hospital during 1921–32. Only 10 of every 100 cases were submitted to partial gastrectomy, and 7 out of these 10 survived the operation. The possibilities of improving the proportion of operative cures is discussed.

DOUBLE GALL-BLADDER. REPORT OF A CASE AND REVIEW OF 38 CASES. By E. Stolkind (London). The specimen described was obtained at autopsy. It had caused no symptoms. There was a septum of congenital origin dividing the gall-gladder into two equal loculi. The reported cases are analysed.

SUBMARINE SALVAGE. By Surgeon Lieut.-Comm. S. Jenkinson.

DEEP DIVING. By Surgeon Lieut.-Comm. P. K. Fraser.

There are also short notes on rare and obscure cases, and an appreciation of the life and work of Wilfred Trotter.

Births, Marriages and Deaths

BIRTHS

ELLIOT-SMITH.—On May 16, at Oxford, the wife of Mr. Arthur Elliot-Smith, F.R.C.S.—a son.

LISTER.—On May 20, at Bishop's Stortford, the wife of Major Arthur Lister, F.R.C.S., R.A.M.C.,—a daughter.

MCSWEENEY.—On May 13, in Dublin, the wife of Dr. C. J. McSweeney—a son.

RENDALL.—On May 20, at High Wycombe, the wife of Surgeon Lieutenant D. C. Shuttleworth Rendall, R.N.V.R.—a daughter.

STEVENS.—On May 15, in Jersey, the wife of Dr. A. E. Stevens—a son.

WINDER.—On May 16, in London, the wife of Dr. Anthony Winder, of Westerham—a daughter.

MARRIAGES

HAWKINS—SLADEN.—On May 18, at Haddenham, Bucks, Gerald Francis Cæsar Hawkins, B.M., Lieutenant, R.A.M.C., to Patricia Enid Lambart Sladen, of Princes Risborough.

DEATHS

CROSBY.—On May 18, Herbert Thomas Crosby, M.B. Camb. of Gordon Square, W.C.1.

GOLDSMITH.—On May 19, at Aldeburgh, Suffolk, George Harvey Goldsmith, M.D. Camb., aged 72.

HUMPHRY.—On May 17, at Abergavenny, Gilbert Percy Humphry, M.R.C.S.

KELYNACK.—On May 17, at Harpenden, Violet Kelynack, M.B. Edin.

LEVACK.—On May 16, in Norwich, John Sutherland Levack, M.B. Edin., D.M.R.E., aged 53.

MOWLL.—On May 15, in London, Christopher Kilvinton Mowll, M.R.C.S.

PATERSON.—On May 21, in Glasgow, Herbert John Paterson, C.B.E., M.D., M.Chir. Camb., F.R.C.S., of Berkhamsted, aged 73.

RUSSELL.—On May 19, at Instow, Devon, George Blakeley Russell, M.B. Dubl., Major, R.A.M.C. (retd.), aged 79.

ST. AUBYN-FARRER.—On May 20, Claude St. Aubyn-Farrer, F.R.F.P.S.

STEPHENS.—On May 18, at Emsworth, Hants, Lockhart Edward Walker Stephens, C.B.E., M.R.C.S.

TAYLOR.—On May 14, at Perth, William Atkinson Taylor, M.B. Edin., aged 69.

Appointments

DICKINSON, H. J. L., B.M. Oxfd, casualty medical officer at the West Middlesex County Hospital.

KAY, E. JEAN, M.B. Edin., temporary first assistant medical officer at King Edward VII Sanatorium, Hertford Hill, Nr. Warwick.

KEANE, C. A., M.R.C.S., D.P.M., medical superintendent at Northampton County Mental Hospital, Berrywood.

ROSE, W. L., M.B. Sheff., clinical pathologist at the Children's Hospital, Sheffield.

SCOTT, E. D., M.D. Lond., M.R.C.P., hon. physician to the King Edward VII Memorial, Eliot Hospital, Haywards Heath.

STANFORD, SYDNEY, M.B. Lpool., resident surgical officer at Mount Gold Orthopædic and Pulmonary Tuberculosis Hospital, Plymouth.

STEVENSON, D. LANG, F.R.C.S.E., resident assistant surgeon at the David Lewis Northern Hospital, Liverpool.

WILLS, K. L., M.B. Camb., temporary hon. physician to the skin department of the Willesden General Hospital.